The Thesis Committee for Charles Aaron Seipp
Certifies that this is the approved version of the following thesis:

The Total Synthesis of (±)-Cepharatine A

APPROVED BY
SUPERVISING COMMITTEE:

Supervisor:

Philip Magnus

Sean Kerwin

The Total Synthesis of (±)-Cepharatine A

by

Charles Aaron Seipp, B.A.

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Dedication

First and foremost, I would like to thank my parents Michele and Frank Seipp. You both have provided me with years of love, care, and support. I really would not have made it this far in life if it had not been for your amazing parenting and constant support. Thank you very much! I love you both dearly!

Dr. Magnus, thank you for the mentorship and friendship over the years. You taught me most of what I know about synthetic chemistry and definitely imparted upon me your enthusiasm for it all.

Last but not least, I definitely need to thank the Magnus lab. Bahman- you provided me with two years of support and help. When I was unsure how to run something, I knew I could always come to you for assistance. Will, Tim, Kyle, and Alan- you guys were always there to talk some chemistry and give me some amazing input. Furthermore, your friendship and the jovial atmosphere you all created made the time honestly fly.

Abstract

The Total Synthesis of (±)-Cepharatine A

Charles Aaron Seipp, M.A.

The University of Texas at Austin, 2013

Supervisor: Philip Magnus

The hasubanan alkaloid cepharatine A, was efficiently synthesized in 8 steps from commercially available starting materials in overall 16% yield. Highlighted in this synthesis, is a tandem phenolic alkylation – annulation which formed both a quaternary center as well as an unsaturated ring. This key step allowed for rapid construction of the core of the molecule. Subsequent reductive amination and acid catalyzed cyclization afforded the title compound.

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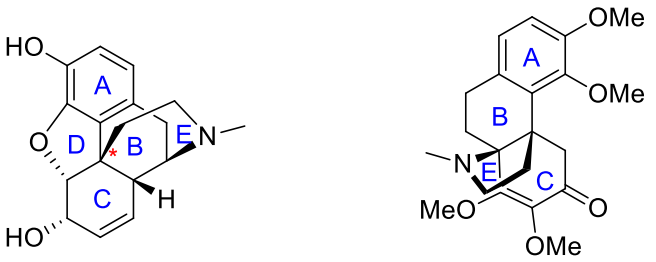
Chapter 1: The Hasubanan Alkaloids and Cepharatine A

1.0 INTRODUCTION

The hasubanan alkaloids are a class of natural compounds bearing close structural resemblance to the morphinan alkaloids **(Figure 1)**.[i]



(-) morphine (1) **(-) hasubanonine (2)**

Figure 1: A comparison of the structure of representative alkaloids from the morphinoids and the hasubanan alkaloids.

Since the discovery of the first hasubanan alkaloid, hasubanonine, in 1951, dozens of additional compounds in this unique class of molecules have been discovered. [i,ii] This class of molecules remains interesting from both a chemical and a biological perspective. Chemically, these structures are very complex and are an attractive synthetic target because they are composed of a functionally dense tetracyclic ring system and a quaternary carbon center. Biologically, it was thought that the hasubanan alkaloids may have potent analgesic properties based their close structural similarities to the morphinoids alkaloids. As a result, much of the initial research into the discovery and the syntheses of these molecules first took place to explore their potential analgesic properties. As of this time, there have been no reported analgesic effects from any of the hasubanan alkaloids; however, it has been hypothesized that this may be due to the antipodal nature of the hasubanan alkaloids when compared to the morphinoids. That is, the hasubanan

alkaloids and the morphinoids both have opposite absolute stereochemistry. This observation lead Schultz *et. al.* to propose that the unnatural enantiomers of the hasubanan alkaloids may show bioactivity.[iii] As the isolated compounds all existed as the "wrong" enantiomer, it is possible that the unnatural enantiomer may have the desired analgesic effects.

1.1 CEPHARATINE A

In 2011, Guan *et. al.* added to the list of known hasubanan alkaloids when he isolated a new series of hasubanan alkaloids, cepharatines A-D, from the plant *Stephania cepharantha* **(Figure 2)**.[iv]

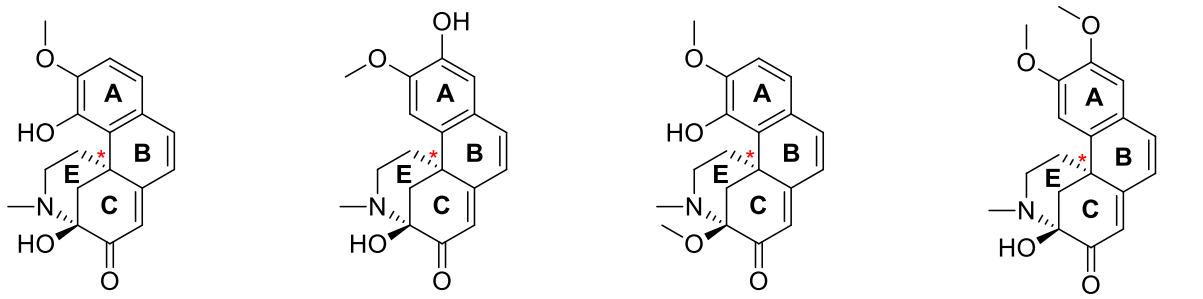


Figure 2: The structures of cepharatines A-D as isolated by Guan, 2012.

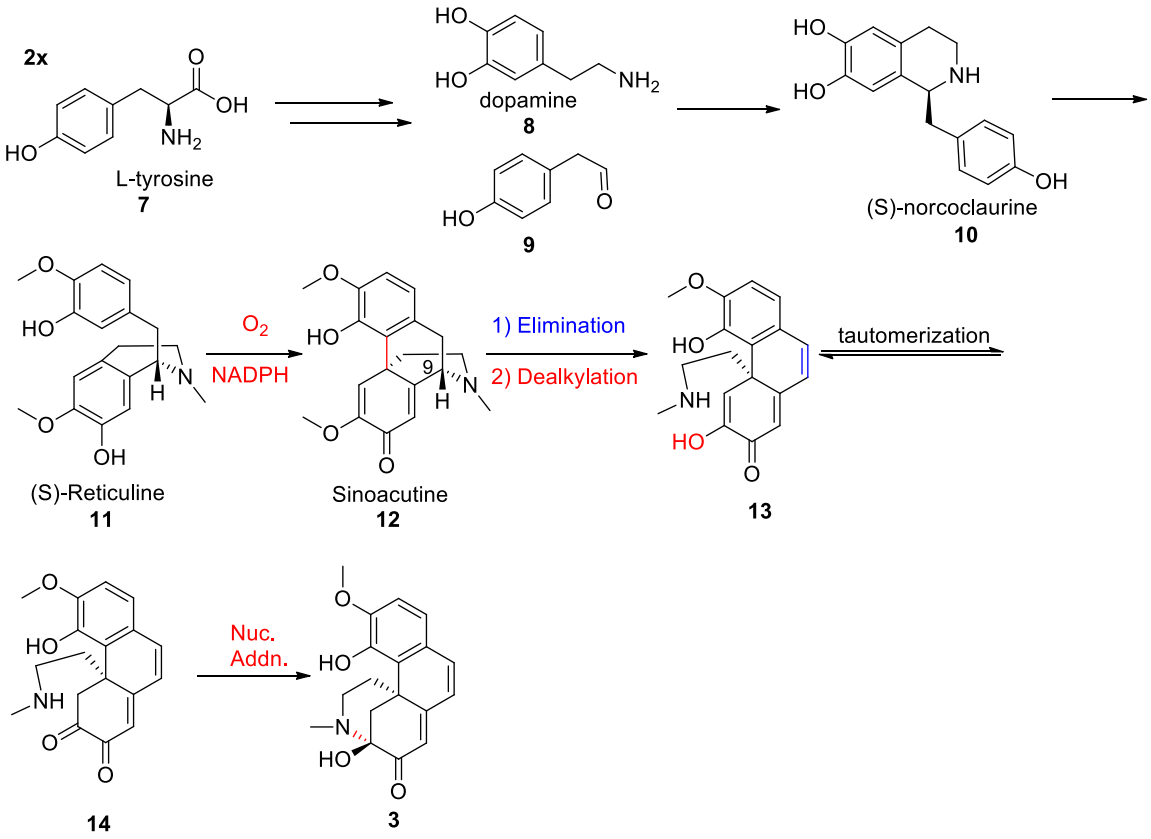
This plant has been used in Chinese folk medicine for the treatment of gout, rheumatism, and edema by the Miao people, and because of this people wondered what constituents of the plant may have medicinal properties. Guan et. al. obtained a sample of the plant from the Guizhou Province in China, dried the sample, and powdered it. Extraction into ethanol followed by subsequent removal of solvent yielded a residue which was separated by column

chromatography. Subsequent analysis of the pure fractions gave rise to four unique compounds, cepharatines A-D. A crystal structure of cepharatine A was obtained to confirm its structure.

From a synthetic standpoint, all four of these compounds were interesting targets. First and foremost, these compounds each have a densely functionalized tetracyclic ring system and a quaternary carbon center. Even with the current advances in synthetic chemistry, there is still no efficient way of generating the cores of these molecules. Secondly, the potential for analgesic properties warranted an investigation of these alkaloids. Finally, there has been no known synthesis of the unnatural enantiomer of the compound. While all four structures were of interest to our laboratory group, it was ultimately decided to focus on cepharatine A as Guan et. al. had obtained a crystal structure of this molecule. The crystal structure provided unambiguous identification which gave us confidence to begin a synthetic effort towards its construction.

1.2 The Biosynthesis of Cepharatine A

While the biosynthesis of the cepharatine alkaloids is still under investigation and a topic of much debate, they are commonly thought to arise from the common biosynthetic intermediate sinoacutine (**Scheme 1**).[v,vi, vii,iv]



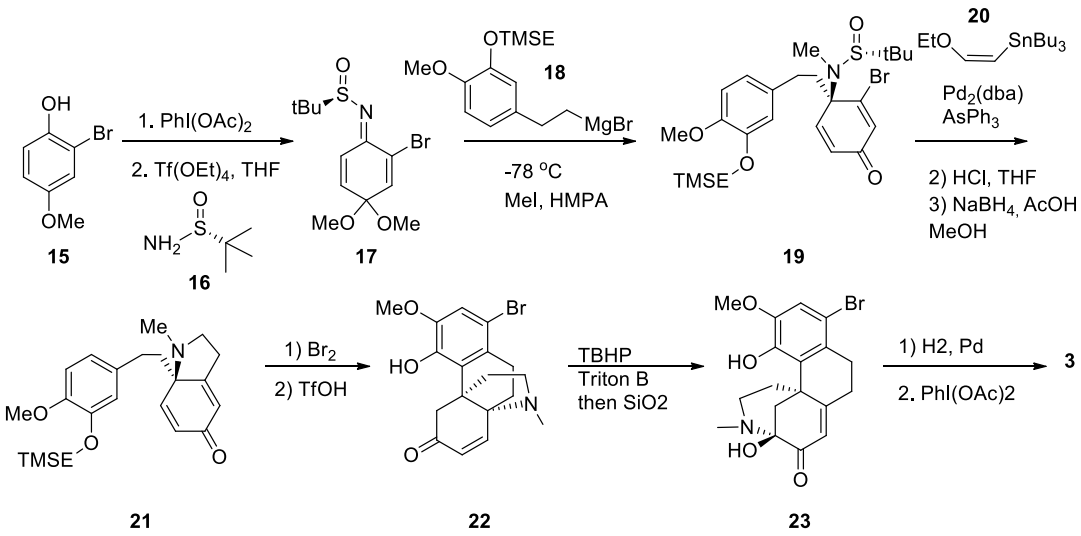
Scheme 1: The proposed biosynthesis of cepharatine A from *L*-tyrosine.

Two molecules of L-tyrosine are transformed into dopamine and aldehyde **9**. A Pictet-Spangler like enzymatic coupling of these two molecules gives rise to (S)-norcoclaurine. Enzymatic addition of another phenolic hydroxyl, and subsequent methylations yields (S)-reticuline. In the biosynthesis of the morphinoids, the stereochemistry of (S)-reticuline is inverted to (R)-reticuline prior to the oxidative coupling. In the case of the hasubanan alkaloids, the oxidative phenolic coupling proceeds on (S)-reticuline, giving rise to sinoacutine. This failure to "correct" the stereochemistry of (S)-reticuline is ultimately what gives rise to the antipodal stereochemistry of the hasubanan alkaloids. From here, it is proposed that sinoacutine undergoes the elimination of the C9- nitrogen bond, followed by demethylation of the methoxy group on the C ring. This

allows the tautomerization of dienone **13** to the extremely reactive diketo species **14**. Nucleophilic addition of the secondary amine, followed by a proton transfer step, yields cepharatine A.

1.2 PREVIOUS SYNTHESIS

Due to the recent discovery of the cepharatines, few total syntheses have been published. Of note is Reisman *et. al's* synthesis of (-)-cepharatine A, which utilized a novel Friedel crafts-like addition to generate the core structure of the molecule (**Scheme 2**).[viii]



Scheme 2: Reisman et. al's total synthesis of (-) cepharatine. The key Friedel-Crafts alkylation afforded the coupling of the **A** and **C** rings of cepharatine.

Reisman began her synthesis by forming sulfinimine **17** through the reaction of bromophenol **15** and *N-tert*-butanesulfinimine. The chirality of the sulfinimine allowed for the stereoselective addition of Grignard **18,** generating dienone **19**, and thus constructing both the **A** and **C** rings of cepharatine A. Next, a Stille coupling installed an unsaturated center that upon cleavage of the

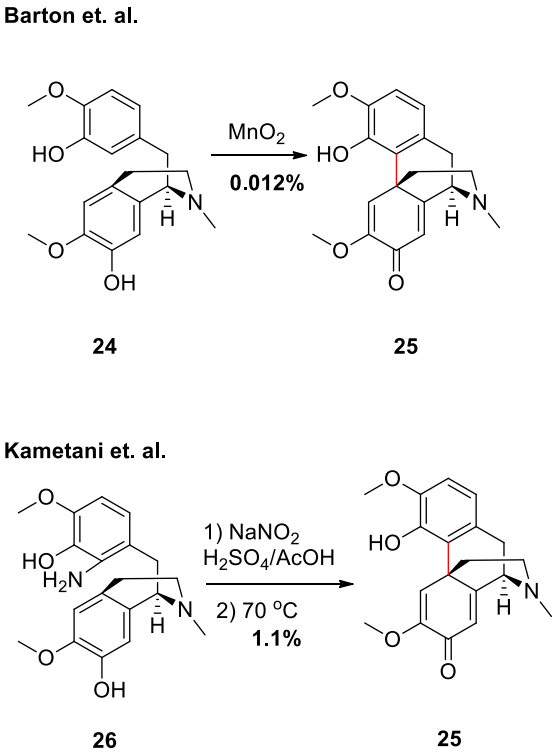
sulfinimide with aqueous HCl, underwent an intramolecular condensation. Subsequent reduction with sodium borohydride yielded dienone **21**. While three rings of the tetracyclic ring system of were already installed, it was still necessary to couple the **A** and **C** rings. Instead an oxidative phenolic coupling analogous to the proposed biosynthetic pathway, a Friedel-Crafts alkylation afforded the desired bond formation. First, bromination of the arene provided a necessary blocking group that prevented the reaction from giving the undesired regioisomer. Next, TfOH deprotected the phenol, providing an electron rich arene nucleophilic enough to readily undergo addition to the enone yielding compound **22**. While all four rings were installed, the **E** ring was connected to the wrong carbon in the molecule, thus a rearrangement was necessary. Treatment of enone **22** with TBHP, Triton B, and SiO_2 afforded enone **23**, establishing the regiochemistry seen in cepharatine A. Reductive debromination, followed by formation of the C9-C10 olefin with $PhI(OAc)_2$, afforded **3** in 10 steps in an overall 10% yield.

Utilizing this general synthetic scheme, Reisman *et. al.* was also able to enantioselectively synthesize (-)-cepharatine C, D, as well as (-)-8-demethoxyrinanine. While both enantioselective and concise, no synthesis of the unnatural enantiomer of cepharatine A was produced. As the unnatural enantiomer potentially has analgesic properties, it would be worthwhile to synthesize it. Furthermore, while concise it can be argued that this synthesis is not ideal. One of the major detractions from this route is that the molecule is not kept in the correct oxidation state throughout the synthesis. There are many late stage oxidations and reductions needed to furnish the final product, adding steps and decreasing the overall yield. Thus, a total synthesis was envisioned that would not only be able to provide (+)-cepharatine A, but also would avoid these unnecessary late stage changes in oxidation state.

Chapter 2: The Synthetic Strategy

2.0 The Oxidative Phenolic Coupling

In the biosynthesis of cepharatine A, *Stephania Cepharanthia* first forms the C-N bond in reticuline, and then undergoes an oxidative phenolic coupling. While this may seem an expedient way to synthesize this molecule, in practice this reaction is exceedingly difficult to reproduce synthetically. In many of the early syntheses of morphinoids this route was attempted; however, the yield of the key coupling was low at best **(Scheme 3)**. [ix,x]

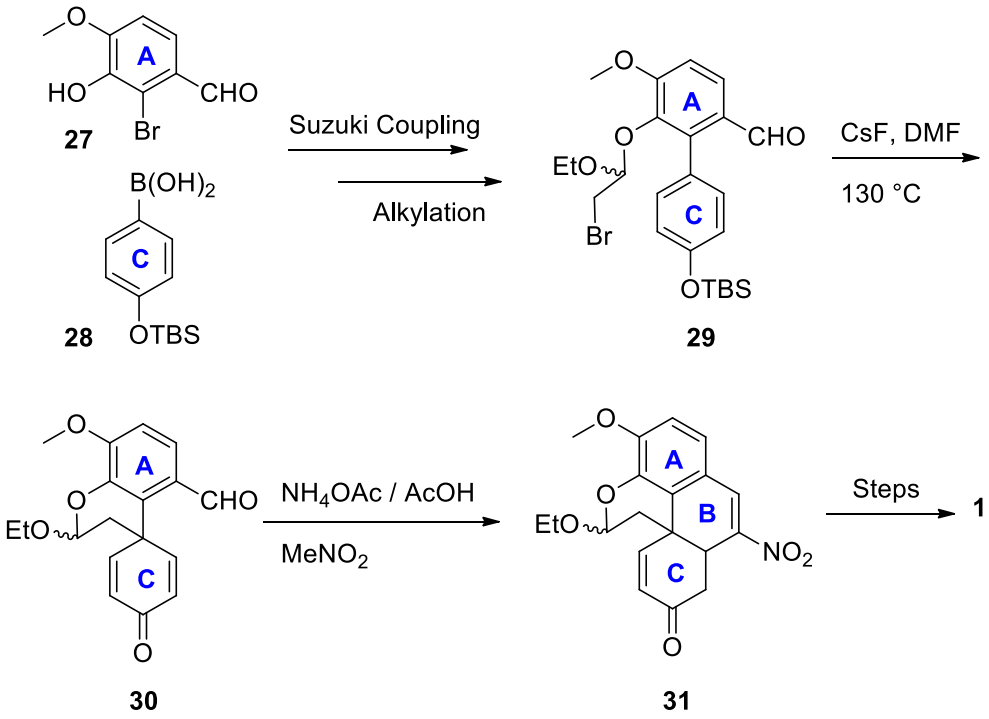


Scheme 3: Two attempts in the total syntheses of morphinoids to harness the power of the phenolic oxidation. Both proceeded in poor yields.

Barton's MnO_2 oxidation of reticuline to salutaridine proceeded in only 0.012% yield, while Kametani's azo coupling was optimized at a 1.1% yield. Though it may be possible to find a

reliable and high yielding way of performing this transformation it would be prudent to find an alternative route.

Knowing that **3** shares a common core with morphine, we looked back at the phenolic alkylation strategy that Magnus *et. al.* used to set the quaternary center of morphine. In the total synthesis of (±)-morphine and (-)-galanthamine, they were able to effect this overall transformation by swapping the order of the steps in the biosynthesis; by utilizing a Suzuki coupling to couple the **A** and **C** rings instead of an oxidative phenolic coupling, they were able to use a high-yielding phenolic alkylation to form the quaternary center **(Scheme 4)**.[xi]



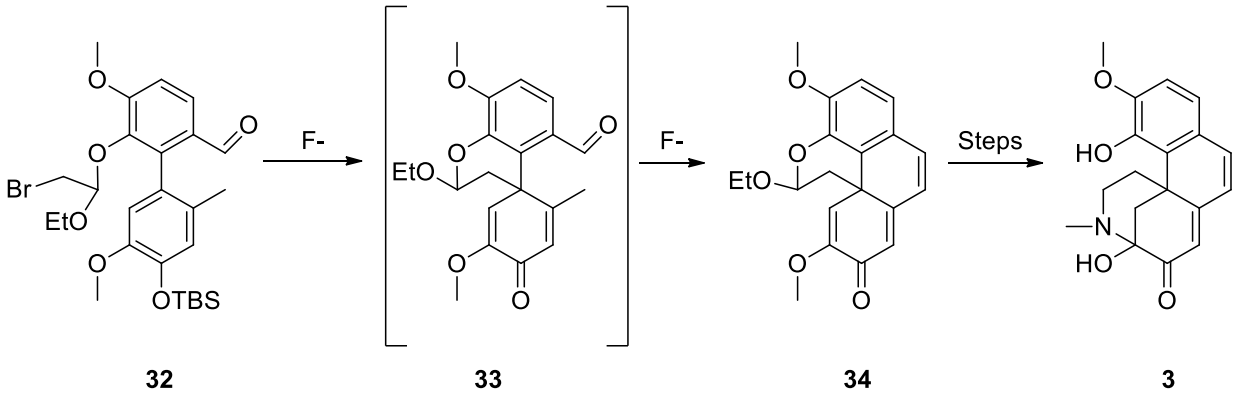
Scheme 4: In Magnus *et. al.'s* synthesis of morphine, the key phenolic alkylation set not only the quaternary center but also the functional handles needed for generation of the rest of the codeine core.

The **A** and **C** rings of morphine were first installed utilizing a Suzuki coupling. Subsequent alkylation yielded acetal **29,** which underwent a phenolic alkylation in the presence of CsF at 130

ºC to give dienone **30.** Next, Henry conditions yielded nitro alkene **31**. From this phenolic alkylation and subsequent Henry reaction, many structural features were gained. First and foremost, the quaternary center was formed in high yield. Furthermore, the formation of the **B** ring was able to occur while also installing the nitro group which was later reduced in order to the amine in the **E** ring. Finally, upon removal of the acetal, the **D** ring would easily form via an intramolecular conjugate addition accelerated by the conformation of the molecule.

2.1 RETROSYNTHESIS

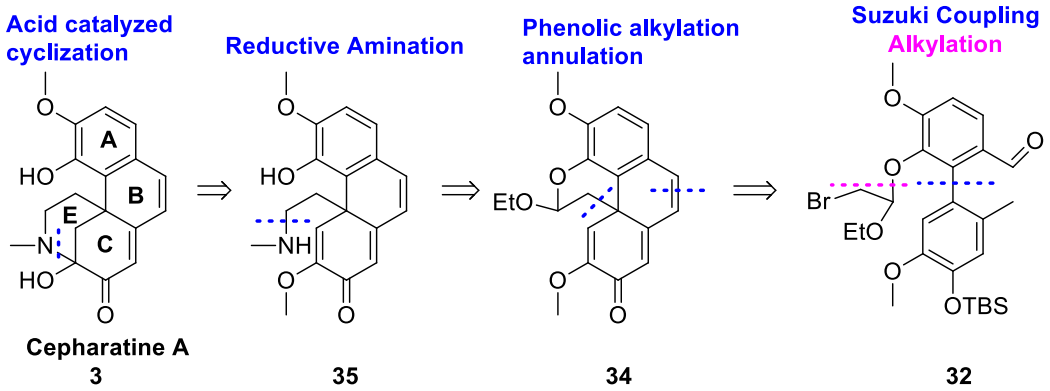
This methodology, while exceptionally efficient, needed to be modified slightly for the total synthesis of cepharatine A. After all, cepharatine has a different connectivity for the **E** ring, as well as no **D** ring and an olefin at C9-C10. We postulated that, if a methyl group was added to the bottom ring, we could modify this reaction to not only generate the quaternary center but also generate the **B** ring of cepharatine A, affording the requisite olefin. We reasoned that the initial phenolic alkylation would generate an acidic vinyl methyl group, which could subsequently be deprotonated by the CsF and nucleophilicly attack the proximal aldehyde **(Scheme 5)**.



32 **33** **34** **3**

Scheme 5: Hypothesized mechanism for the tandem phenolic alkylation – annulation planned for the generation of the quaternary center in the total synthesis of cepharatine A.

This tandem phenolic alkylation – annulation would generate three rings and set the quaternary center using a minimal number of steps. A synthesis designed around this key step was devised (**Scheme 6**).



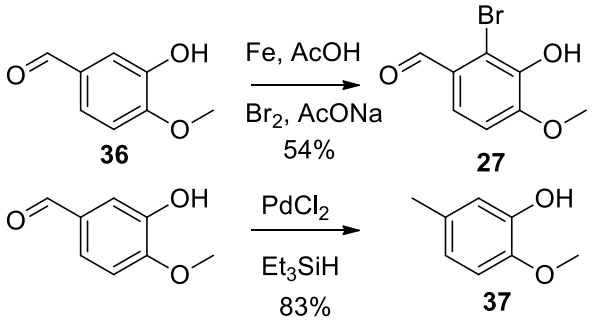
Scheme 6: The retrosynthesis of cepharatine A.

Retrosynthetically, a concise method to cepharatine A was envisioned. It was realized that biaryl **32** could be easily obtained via a Suzuki coupling to quickly form the **A** and **C** rings of cepharatine. A simple alkylation utilizing ethyl vinyl ether would generate the functional handle needed to install both the B ring and the quaternary carbon center upon exposure to cesium fluoride to generate dienone **34.** It was expected that this key step would proceed by first generating the quaternary center. This transformation would turn the aryl methyl group into a much more acidic beta vinylic methyl, allowing deprotonation by excess cesium fluoride and subsequent annulation. Reductive amination of the protected aldehyde with methyl amine will afford dienone **35,** which can be cyclized to **3** under acidic conditions.

Chapter 3: The Total Synthesis of Cepharatine A

3.0 The Initial Steps

The synthesis of cepharatine A was started exclusively from isovanillin **(Scheme 7)**.



Scheme 7: Isovanillin provided the starting material for both of the required phenols.

While both **27** and **37** are commercially available, isovanillin is an extremely inexpensive starting material that is readily available as a byproduct of the paper manufacturing process. Isovanillin **(36)** was regioselectively brominated using iron, bromine, and sodium acetate to give bromophenol **27** in 54% yield. It was also realized that through hydrogenolysis of the aldehyde, it would be possible to obtain the required methyl substituted phenol **37**. Unfortunately, initial attempts at this transformation gave mixed results. Initially, 10% palladium on carbon in methanol with a catalytic amount of hydrochloric acid was attempted at atmospheric pressures. A yield of 44% was obtained, but this was not easily reproduced. Over the next several attempts, yields ranging from 0% to 60% were obtained. Varying the concentration of HCl, the solvent, the source of the acid (AcOH, $HClO_4$), or utilizing Pearlman's catalyst did little to influence the results. Furthermore, despite purification by silica plug, samples obtained by this methodology

turned black and became unrecognizable by NMR presumably due to residual Pd/C. Thus an alternative method for this transformation was sought. Transfer hydrogenation utilizing anhydrous ammonium formate as a hydrogen source gave no observable product. In searching the literature, it was discovered that transfer hydrogenations occur readily utilizing triethyl silane and palladium chloride, presumably through a palladium-silane intermediate (**Figure 3**).[xii]

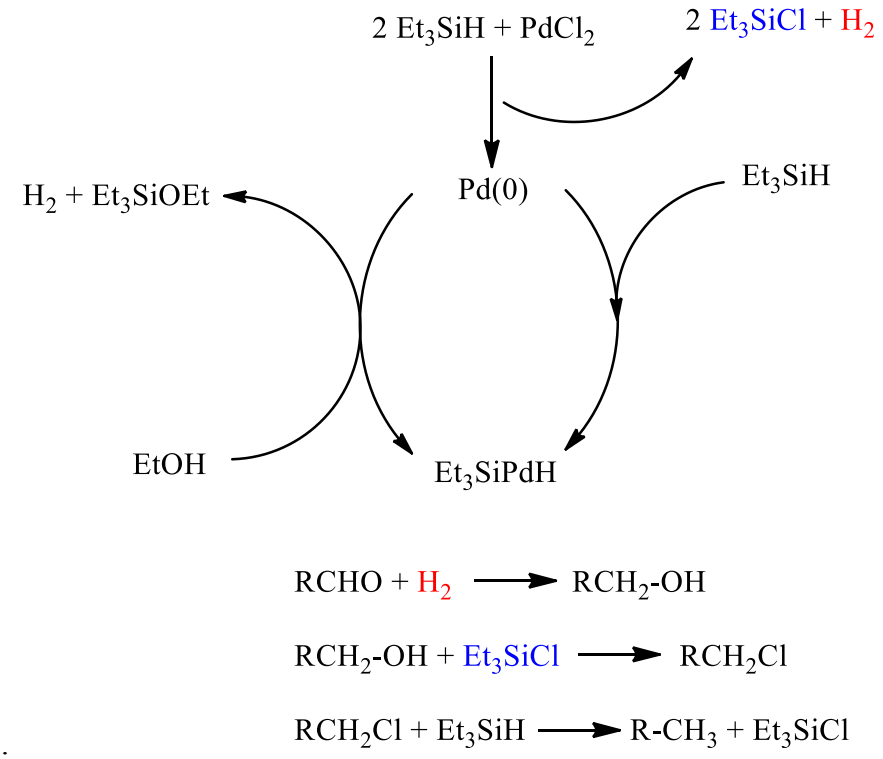
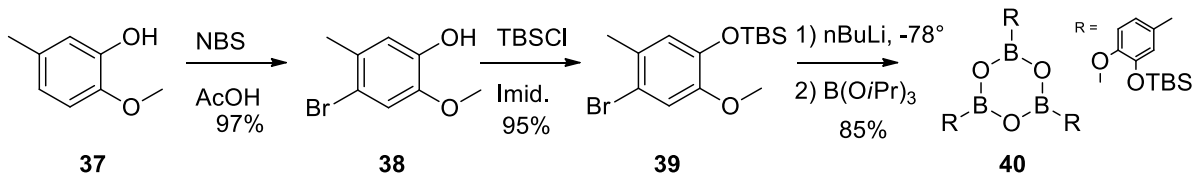


Figure 3: Proposed catalytic cycle for the transfer hydrogenation of isovanillin in the presence of palladium (II) chloride and triethyl silane.

When applied to the isovanillin system, the desired phenol was obtained in an 83% yield. More importantly, the reaction was easily reproducible and scalable, giving ready access to the desired compound. With **37** in hand, the rest of the coupling partner was synthesized **(Scheme 8)**.

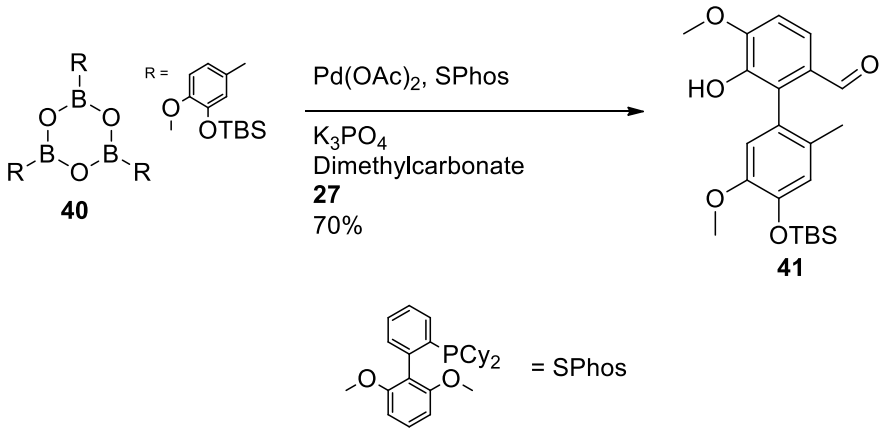


Scheme 8: Generation of the boroxine trimer.

Phenol **37** was regioselectively brominated and sequentially protected using TBSCl to give compound **39**, which underwent halogen – metal exchange with *n*BuLi, and reacted with triisopropyl borate to yield boroxime **40.** Interestingly, the ^{1}H- NMR of the trimer shows three distinct sets of peaks, each presumably corresponding to a different rotamer of the compound. Upon heating at 60 ^{o}C for an hour, the NMR coalesced into a single spectrum.

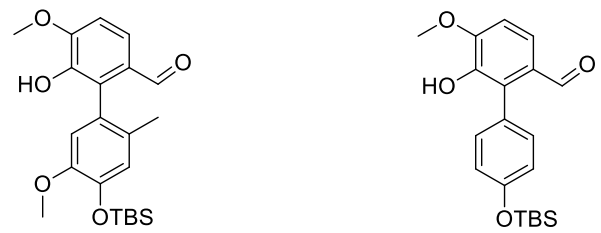
3.1 THE SUZUKI COUPLING

With the boroxine in hand, attempts were made to couple **27** and **40** to afford biaryl **41.** **(Scheme 9).**



Scheme 9: Suzuki coupling of the **A** and **C** rings.

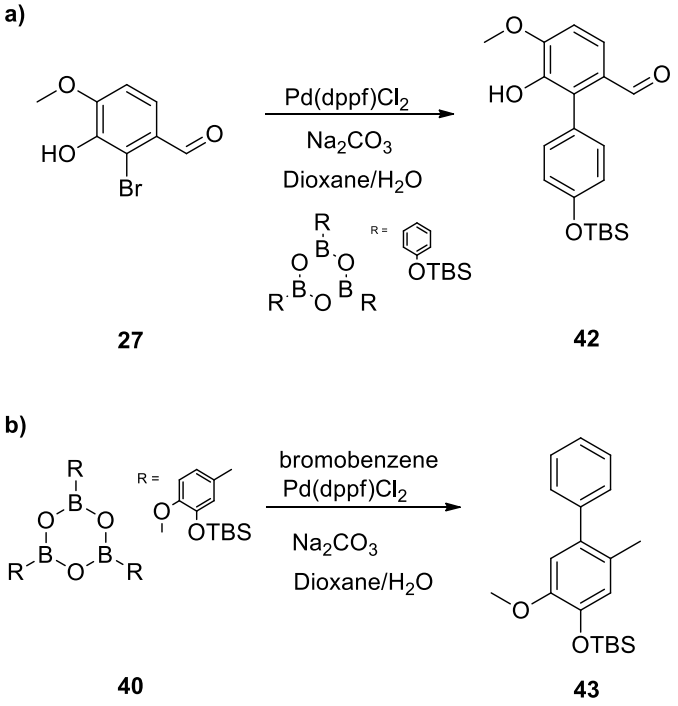
Initial attempts revolved around the use of $Pd(dppf)Cl_2$, in a dioxane/water mixture heated to reflux. Unfortunately, after several attempts not even trace product was observed by LCMS. In an attempt to grasp what the problem could be, a myriad of different conditions were attempted. In the Magnus *et. al.* synthesis of morphine and galanthamine, a $Pd_2(dba)_3$ / $P(cyc)_3$ system was used to afford a very similar biaryl (**Figure 4**).



41 **42**

Figure 4: Comparison of the cepharatine biaryl (left) vs. previously synthesized biaryl (right).

Unfortunately, this reaction gave no product. The only thing isolable from the mixture were both starting materials, as well as significant amounts of protodeborylated trimer. In order to discount the possibility that the trimer or the isovanillin derivative were not good or contained impurities that would hinder a Suzuki reaction, two control reactions were undertaken (**Scheme 10**).



Scheme 10: Control reactions to make sure that **(a)** the 2-bromoisovanillin and **(b)** the boroxine trimer were both competent Suzuki coupling partners.

Both control reactions showed generation of product by LCMS analysis. Thus, we were able to determine that the problem did not lay in the reagents (or some impurity present in them) but in the reaction conditions itself.

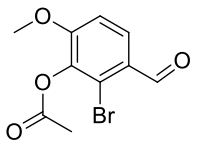
When one compares the two structures of the desired biaryl, the only differences between the two is the presence of the methyl group and a methoxy group on the boroxime needed for cepharatine A. As electron donating substituents on the borate increase the rate of the Suzuki coupling, the methoxyl most likely increases the rate of reaction and does not play a role in our observed problems. Thus, the cause of the issues fall solely upon the addition of the methyl group. While one would not usually consider an additional methyl group a substantial amount of

steric hindrance, it is well known that Suzuki reactions containing three or four substituents ortho to the coupling site proceed only sluggishly, if at all.[xiii] This is particularly true if there is a substituent ortho to the boronic acid. In the case of the present Suzuki system, there are three ortho substituents to the coupling center. It was thus decided that more forcing conditions were needed if this reaction were to proceed in an appreciable yield. Initially, attempts were made to vary the base strength, as strong bases have been shown to help in the coupling of sterically hindered Suzuki reactions.[15, xiii] Unfortunately, K_3PO_4 was the strongest base able to be tolerated without seeing substantial degradation presumably due to negative interactions with the aromatic aldehyde. In and of itself, the usage of K_3PO_4 still generated none of the desired biaryl. Higher temperatures, different solvents, phase transfer catalysts, different ligands and metals were all attempted, each affording no detectable product. In order to try even more extreme conditions, it was decided to utilize a sealed tube so that high pressures and temperatures could be maintained.

The reaction was thus performed in a sealed tube, utilizing DMSO / CH_2Cl_2 at 120 ^oC, utilizing Pd(dppf)Cl_2 as a palladium/ligand source. An 8% yield was obtained, along with significant amounts of observed protodeborylation. While a low yield of product, this provided useful data. First, more forcing conditions were in fact capable of producing the coupling. Secondly, it gave a pure sample of product, which allowed for quick qualitative determination of reaction efficacy by TLC. Other solvents were tried in order to improve the yield, including 1,2 dimethoxy ethane, pure DMSO, as well as DMF, but none were able to improve upon the 8% yield displayed previously.

In running these reactions, it was noticed that upon addition of the base, the bromoisovanillin would turn a canary yellow color. This was reversible upon addition of dilute acid and was thus hypothesized to be due to the deprotonation of the phenol. A literature search

was performed in order to find other examples of unprotected *o*-phenols being coupled in Suzuki reactions. Unfortunately, few examples were found, and those that had been performed worked mostly in poor yield, save a few isolated examples. It was hypothesized that the deprotonation of the *o*-phenol may be playing a role in the decreased reaction rate, and thus the phenol was summarily masked using an acetate **(Figure 5)**.

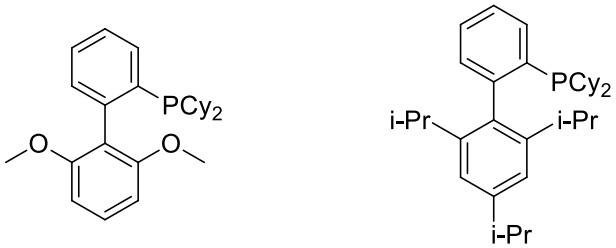


44

Figure 5: Structure of the acetate protected phenol.

Subjecting acetate **44** to the Suzuki coupling reaction in DME gave the desired biaryl in 29% yield. While the yield had been substantially increased, trouble deprotecting the acetate in the presence of the labile phenolic TBS group forced abandonment of this approach in favor of optimizing the reaction on the unprotected phenol.

While further searching for potential solutions to overcome the problems associated with the steric bulk of our coupling partners, several reviews published by Buchwald *et. al.* were obtained where he advocated the use of bulky biarylphosphine ligands for the coupling of hindered biaryls **(Figure 6).**[xiv]



SPhos **XPhos**

45 **46**

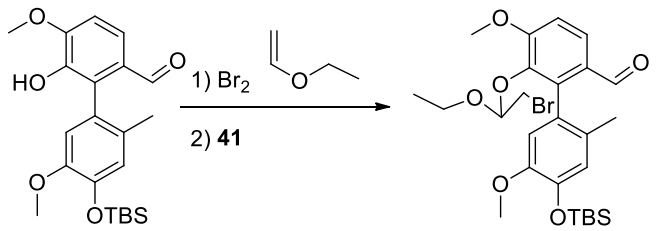
Figure 6: Structure of two of the Buchwald Ligands, SPhos and XPhos.

Buchwald hypothesizes that the steric bulk of the ligand plays a substantial role in the observed reactivity. While it may seem counter intuitive that a bulky ligand would aid in the reaction of sterically hindered coupling partners, it is important to consider the role the bulk of the ligand plays. The bulky ligand makes it extremely unlikely that two ligands will be bound to the palladium. In fact, the bulk drastically increases the equilibrium of the metal-ligand complex so that it favors the mono-ligated species. The mono-ligated palladium complex is a 12 or 14 e^- species (depending on the exact mode of binding of the ligand) and thus would be extremely reactive towards oxidative addition. This enables otherwise slow Suzuki couplings to proceed at drastically enhanced rates. In order to test out the Buchwald ligands, a Suzuki reaction utilizing Xphos and $Pd(OAc)_2$ at 90 ^{0}C in toluene was performed, netting an overall 23% product yield. This was the first time product had been obtained outsides of a sealed tube utilizing either DME or DMSO as solvent. Spurred on by these results, SPhos was also tried, giving an increased yield of 40%.

While the Suzuki coupling was proceeding in usable yields, we were determined to further optimize the reaction. A paper was found demonstrating that dimethyl carbonate could act as a competent reaction solvent for Suzuki coupling reactions.[xv] While their hypothesis that this solvent could afford couplings without the addition of metal was ultimately shown to be incorrect in a subsequent study of theirs, we thought that their data did in fact suggest that DMC could help to accelerate the coupling reaction. In initial tests utilizing a dimethyl carbonate / SPhos system, yields seemed to be drastically improved. When conditions were optimized (RT, 24 hours), this coupling system gave yields upwards of 70%. Unfortunately, no studies were performed as to determine why this drastic increase in yield was observed.

3.2 THE PHENOLIC ALKYLATION – ANNULATION

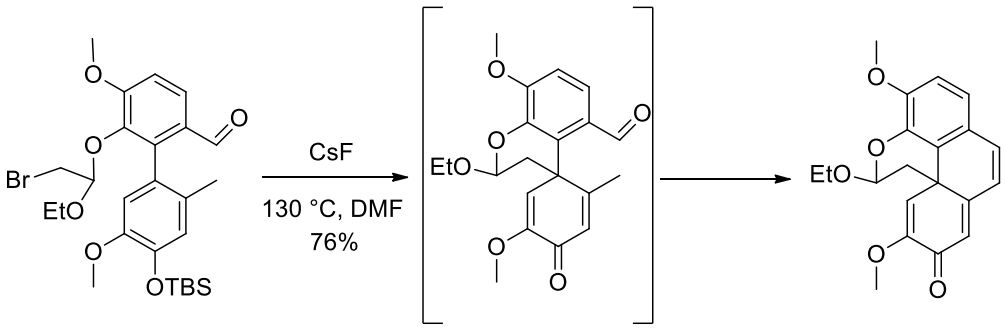
Next, the core of the molecule was to be generated. **41** was alkylated using ethyl vinyl ether and bromine to afford acetal **32 (Scheme 11)**.



41 **32**

Scheme 11: Synthesis of acetal **32**.

When heated with CsF at 130 °C, **32** yielded dienone **34** as a canary yellow solid. We hypothesized that the quaternary center would form first, followed by deprotonation of the newly generated beta vinylic methyl group to form the double bond (**Scheme 12)**.



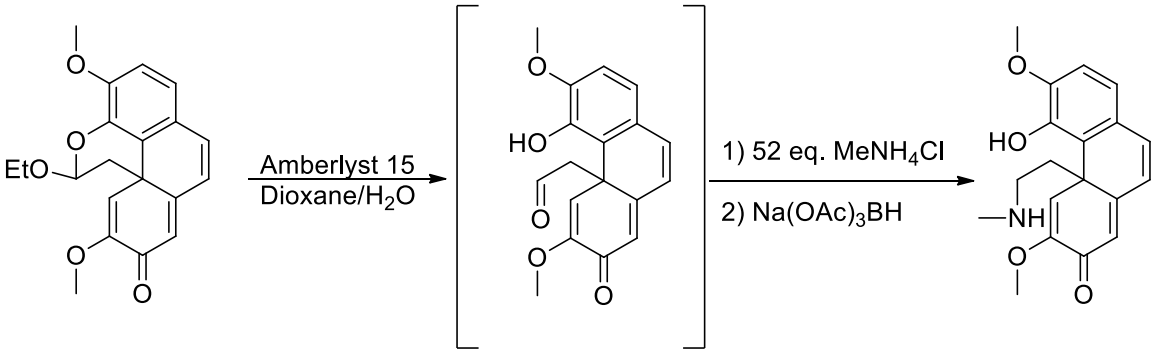
32 **33** **34**

Scheme 12: Synthesis of the quaternary center from biaryl **32**.

While a mechanistic study was not performed, one could observe this two-step reaction taking place. Initially by TLC, one witnessed disappearance of the starting material to afford a colorless UV active spot that was more polar than the starting materials. Upon stirring for another two hours, this newly form spot disappeared, generating a new yellow spot of higher R_f. Overall, this key step proceeded in 76% yield and generated not only the quaternary center of **34** but also the B ring. The structure of the obtained compound was confirmed by x-ray crystallography (see spectral data). A large amount of complexity was generated from this simple reaction, giving us efficient access to the core of cepharatine.

3.3 THE COMPLETION OF CEPHARATINE A

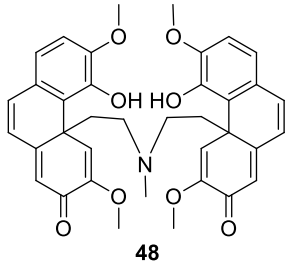
Next, acetal **34** was hydrolyzed to the aldehyde and reductively aminated with methylamine to give amine **35 (Scheme 13)**.



34 **47** **35**

Scheme 13: Reductive amination of the quaternary center to form primary amine **35.**

This step also proved to be problematic, as initial attempts to isolate the unmasked aldehyde showed that it is extremely unstable to ambient conditions, almost completely decomposing during formation and isolation. Furthermore, the reductive amination of the aldehyde utilizing $MeNH_3Cl$ gave predominately dimer **48** as a product, further limiting the utility of this reaction (**Figure 7**).

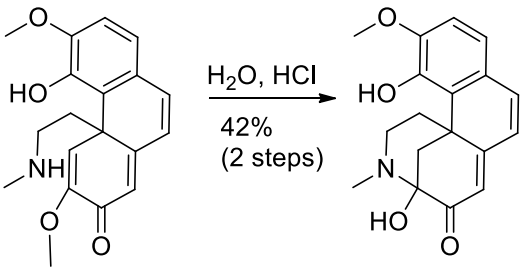


48

Figure 7: The dimeric product formed from the reductive amination of **34**.

To complicate matters further, addition of unhindered basic amines to dienone **34** caused the starting material to turn a deep green and decompose into several unidentified byproducts by TLC. Due to this unexpected decomposition pathway, the amine HCl salt had to be used in this reaction. Utilizing the amine HCl salt in the acidic conditions required to break the acetal further reduced the nucleophilicity of the amine to the point where dimer **48** was the only product. Thus, in order to maximize the yield, it was necessary to break apart the acetal *in situ* to minimize decomposition of the aldehyde yet still provide a nucleophilic source of methylamine that was not so basic as to decompose the **34.** Ultimately, Amberlyst 15 resin was utilized in order to generate the aldehyde *in situ.* The amberlyst was filtered off, leaving behind a neutral solution and a 52 fold excess of $MeNH_3Cl$ pre-dissolved in water was added. After stirring for 10 minutes, triacetoxy borohydride was added to reduce the formed imine. The amine **35** was crudely purified by prep-TLC. In the biosynthesis of cepharatine A, it is thought that the amine is

able to cyclize through reaction diketo intermediate **14**. It was suspected that upon addition of aqueous HCl to **35**, it may be possible to form a species analogous to the diketone intermediate. Thus, amine **35** was then refluxed in dilute hydrochloride acid to generate cepharatine A in 42% yield from the initial formation of the aldehyde **(Scheme 14)**.



35 **3**

Scheme 14: Synthesis of cepharatine A from amine **35**.

Overall, (±) cepharatine A was synthesized in 8 steps from commercially available starting materials in an overall 16% yield. This was accomplished using a tandem intramolecular phenolic alkylation – annulation which proceeded in 76% yield. This methodology has been shown to provide exceedingly facile access to the core of these molecules, and we hope to expand upon the scope in the near future.

Chapter 4: Experimental Conditions and Spectral Data

4.0 General Information

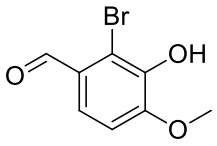
All reagents were purified using standard laboratory methods unless otherwise noted.[xvi] Anhydrous solvents were prepared as follows: CH_2Cl_2 and THF were allowed to sit over sieves for 24 hours and then distilled under a nitrogen atmosphere. Other solvents were purified as noted in the experimental. All reactions were conducted under an argon atmosphere unless noted otherwise.

Reactions were monitored by thin layer chromatography using Merck 60 F_{254} glass-backed silica gel plates. The plates were visualized using either 254 or 365 nm light, or developed using vanillin, ninhydrin, ceric ammonium molybdate, or *p*-anisaldehyde solution. Flash column chromatography was performed using EMD silica gel (particle size of 0.040-0.063).

Melting points were taken on a Thomas-Hoover capillary tube apparatus. Infrared spectra were recorded on a Thermo-Nicolet Avatar 360 FT-IR spectrophotometer. Samples were prepared as neat films on NaCl plates, unless otherwise indicated. ^{1}H NMR spectra were recorded on a Varian spectrometer at 300 MHz or 500
MHz in the indicated solvent and are reported in ppm and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded on a Varian spectrometer at 75 MHz or 125 MHz or 150 MHz in the solvent indicated and referenced internally to the residually protonated solvent. Mass spectra were obtained on a VG ZAB2E or a Finnigan TSQ70.

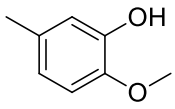
4.1 Experimental Conditions and Compound Data

2-bromoisovanillin (27)[xvii]



Br_2 in 5 mL of acetic acid was added dropwise to a solution of isovanillin (4 g, 26.3 mmol), iron powder (.12 g, 2.14 mol), and sodium acetate (4.33 g, 52.76 mmol) in 24 mL of acetic acid. After all starting material was consumed as justged by TLC, the mixture was poured onto ice water. The precipitate was collected and washed with cold water. The crude material was recrystallized in EtOH to afford (3.27 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (1H, s), 7.62 (1H, d, J = 8.7), 6.96 (1H, d, J = 8.7), 6.09 (1H, s), 4.03 (3H, s)

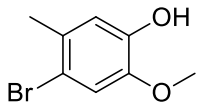
2-methoxy-5-methylphenol (37) [xii]



Isovanillin (5 g, 0.032 mol), triethylsilane (12.6 mL, 0.079)was dissolved in 125 mL of EtOH. $PdCl_2$ (50 mg, 0.282 mmol) was added to the flask in one portion. Reaction was monitored by TLC. Upon consumption of starting materials, reaction was concentrated under vacuum and purified by flash column chromatography (90:10 Hexanes:EtOAC) to afford 3.72 grams of **2**

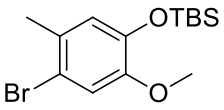
(83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (2H, m), 6.65 (1H, d, J = 7.2), 3.86 (3H, s), 2.26 (3H, s).

4-bromo-2-methoxy-5-methylphenol (38)[xviii]



To a solution of isocreosol (10 g, 72 mmol) in AcOH (144 mL) was added *N*-bromosuccinimide (13.13 g, 74 mmol) in AcOH (343 mL) dropwise over one hour. The reaction was allowed to run for 4 hours. The mixture was concentrated *in vacuo* to roughly one third of the original volume before ice was added and the solution was neutralized with 6 *M* NaOH, causing the product to precipitate. The product was extracted with CH_2Cl_2 and subsequently purified by flash column chromatography (70:30 Hexanes:EtOAc) to afford the product as a white solid (15.1 g, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (1H, s), 6.83 (1H, s), 5.47 (1H, s), 3.88 (3H, s), 2.31 (3H, s).

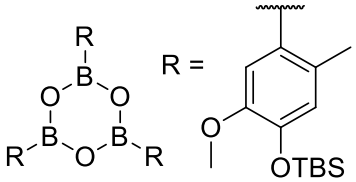
(4-bromo-2-methoxy-5-methylphenoxy)(tert-butyl)dimethylsilane (39)



To a solution of methyl phenol **(1)** (50g, 0.23 mol) in 500 mL dichloromethane was added imidazole (31.31g, 0.36 mol). The solution was stirred for 15 minutes before *tert*-butyldimethylsilyl chloride (38.1g, 0.25 mol) was added in one portion. After all starting

material was consumed, as judged by TLC, the reaction was poured onto saturated aqueous ammonium chloride. The dichloromethane was separated, and the aqueous layer was extracted with ethyl acetate (3X, 50 mL aliquots). The organic phases were combined, and solvent was removed *in vacuo* to yield a viscous yellow oil. Purification by flash column chromatography (SiO2, 30:70 EtOAc:hexanes, slow gradient from pure hexanes) yielded **2** as a clear viscous liquid (72.16 g, 94.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (1H, s), 6.72 (3H, s), 3.77 (1H, s), 2.27 (3H, s), 0.99 (9H, s), 0.14 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ149.7, 144.3, 129.9, 123.0, 116.1, 115.5, 55.8, 25.8, 22.1, 18.5, -4.5 HRMS calcd. for $C_{14}H_{23}BrO_2Si$: 331.07235 (M+) found 331.07212

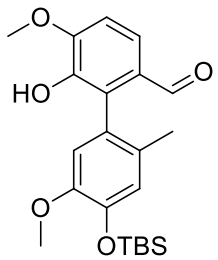
2,4,6-tris(4-((tert-butyldimethylsilyl)oxy)-2-methoxy-5-methylphenyl)-1,3,5,2,4,6-trioxatriborinane (40)[xvii]



To a -78 °C solution of silane **2** (20 g, 0.06 mol) in 100 mL THF was added *n*BuLi(2.4 *M*, 28.8 mL) dropwise. The solution was stirred for 30 minutes. Triisopropyl borate (36.3 mL, 0.193 mol) was added dropwise and the solution was allowed to warm to room temperature and stirred over night. The reaction was quenched with aqueous 10% sodium bisulfate, extracted three times with ethyl acetate (25 mL), and dried with Na_2SO_4. The solvent was removed *in vacuo* and the white solid was purified by flash column chromatography (90:10 Hexanes:EtOAc) to give **3** as a white solid (7.15 g, 85.2 %). IR (thin film): 3226.5, 2957.6, 2927.2, 2857.8, 1558.8, 1512.0, 1465.0, 1339.1, 1275.3, 1206.1, 1151.3, 1109.0, 1053.5 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, s), 6.75 (1H, s), 3.84 (3H, s), 2.73 (3H, s), 1.02 (9H, s), 0.20 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ

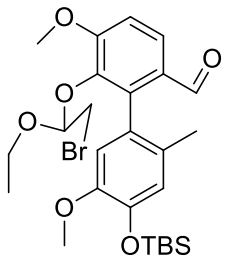
153.0, 152.8, 128.2, 125.0, 59.8, 30.3, 30.3, 26.5, 23.1, 0.0. HRMS calcd. for $C_{42}H_{70}B_{11}O_9Si_3$: 835.4607 (M+1) found 835.4619

4'-((tert-butyldimethylsilyl)oxy)-6-hydroxy-5,5'-dimethoxy-2'-methyl-[1,1'-biphenyl]-2-carbaldehyde (41) [xv,xix]



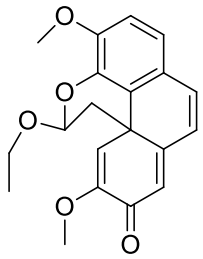
To 100 mL of dimethyl carbonate is added 2-bromo-3-hydroxy-4-methoxybenzaldehyde (3 g, 13.0 mmol**)**, **3** (5.46 g, 19.6 mmol**),** $Pd(OAc)_2$ (60 mg, 0.27 mmol), SPHOS (216 mg, 0.53 mmol), and K_3PO_4 (5.4 g, 25.4 mmol). The solution was allowed to stir for 48 hours. The solvent was removed *in vacuo* and the biaryl was washed with saturated NH_4Cl then extracted with EtOAc (3X, 25 mL). The EtOAc was removed *in vacuo* and the crude product was purified by flash column chromatography (30:70 EtOAc:Hexanes) to afford **4** (3.67 g, 70%) as a pale brown solid. IR (thin film): 3289.3, 2937.9, 2855.0, 1670.0, 1584.6, 1514.9, 1472.7, 1441.0, 1387.9, 1326.1, 1269.9, 1093.9, 1028.6 ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (1H, s), 7.66 (1H, d, J = 8.4), 7.00 (1H, d, J = 8.4), 6.81 (1H, s), 6.66 (1H, s), 5.53 (1H, s), 4.01 (3H, s), 3.74 (3H, s), 1.98 (3H, s), 1.014 (9H, s), 0.20 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 150.3, 148.0, 144.2, 141.7, 130.5, 129.1, 127.4, 123.2, 121.8, 119.5, 113.6, 108.9, 55.3, 54.7, 24.8, 18.2, 17.6, -5.4. HRMS calcd. for $C_{22}H_{31}O_5Si$: 403.19353 (M+1) found 403.19322

6-(2-bromo-1-ethoxyethoxy)-4'-((tert-butyldimethylsilyl)oxy)-5,5'-dimethoxy-2'-methyl-[1,1'-biphenyl]-2-carbaldehyde (32)



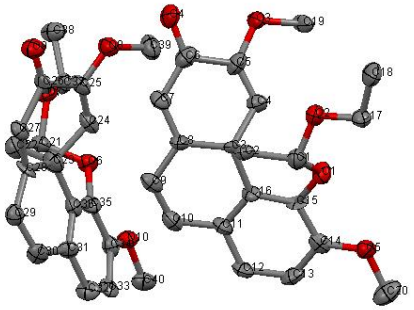
To a solution of Br_2 (.65 mL, 0.012 mol) in CH_2Cl_2 (40 mL) at 0°C was added 1.3 mL ethyl vinyl ether (1.3 mL, 0.014 mol) drop wise until the solution turned colorless. The solution was allowed to stir for 30 minutes before Hunig's base (3.0 mL, 0.017 mol) and **4** (2.14 g, 0.005 mol) were added. The solution was allowed to stir until judged complete by TLC. The reaction mixture was poured onto $NaHCO_3$, extracted with CH_2Cl_2 (3x, 10 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residual oil was purified via column chromatography (SiO2, 30:70 EtOAc:hexanes, slow gradient from pure hexanes) to afford a clear liquid (2.62 g, 89.1 % yield). IR (thin film): 2930.4, 2856.7, 1685.6, 1586.1, 1514.7, 1472.4, 1438.3, 1385.8, 1327.9, 1301.2, 1250.2, 1212.6, 1096.2, 931.4 ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (1H, s), 7.86 (1H, d, J = 8.8), 7.05 (1H, d, J = 8.8), 6.79 (1H, s), 6.70 (1H, s), 6.67 (1H, s), 4.9 (1H, m), 3.97 (3H, s), 3.74 (3H, s), 3.5 (1H, bm), 3.1 (3H, bm), 1.98 (3H, s), 1.07 (2H, m), 1.03 (9H, s), 0.18 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 191.3, 157.7, 157.7, 148.8, 148.7, 145.2, 140.3, 130.1, 130.0, 128.5, 128.5, 125.2, 125.2, 125.1, 125.0, 122.7, 122.5, 115.1, 115.0, 111.3, 111.2, 104.1, 104.0, 64.5, 64.0, 56.1, 56.1, 55.9, 55.7, 31.9, 31.7, 31.6, 25.8, 22.7, 19.4, 19.4, 18.6, 15.1, 15.1, -4.5, -4.5, -4.6 . HRMS calcd. for $C_{26}H_{38}BrO_6Si$: 553.16155 (M+1) found 553.16118

6-ethoxy-3,8-dimethoxy-5,6-dihydro-2H-naphtho[1,2-de]chromen-2-one (34)



A solution of **5** (1 g, 1.8 mmol) under argon in DMF (40 mL) was heated to 80 °C while CsF (1.2 g, 7.9 mmol) was thoroughly flame dried under vacuum. The CsF was quickly added in one portion and the temperature of the reaction mixture was immediately raised to 130 °C. A deep red color was observed immediately upon addition of CsF. Upon completion (as judged by TLC) the mixture was poured onto sodium bicarbonate, extracted into EtOAc (3x, 15 mL), and dried (Na_2SO_4), and concentrated *in vacuo*. ***6*** was isolated via flash column chromatography (30:70 EtOAc:Hexanes), to afford 560 mg (76%) of canary yellow solid. MP (Hexanes:EtOAC) 147-150 °C. IR (thin film): 2974.1, 2932.1, 1653.8, 1627.2,, 1602.8, 1554.5, 1499.0, 1450.5, 1438.8, 1408.2, 1355.8, 1267.5, 1205.0, 1174.5, 1109.3, 1048.6, 998.9, 973.8 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-6.80 (2H, m), 6.70-6.60 (2H, m), 6.43 (1H, d, J = 9.0), 5.62 (.5H, m), 5.13 (.5H, m), 4.25 (.5H, m), 4.03 (.5H, m), 3.90 (3H, s), 3.62 (3H, s), 2.40 (.5 H, m), 2.20-2.00 (1.5 H, m), 1.65 (.5H, s), 1.29 (1.5H, t, J = 8.0), 1.18 (1.5H, t, J = 8.0). ^{13}C NMR (100 MHz, $CDCl_3$): δ181.7, 181.4, 161.7, 161.3, 152.8, 152.3, 151.5, 151.4, 142.5, 141.6, 132.7, 132.2, 128.5, 128.4, 124.5, 124.5, 124.4, 124.3, 123.8, 123.7, 123.6, 123.1, 120.7, 118.8, 111.3, 111.1, 102.0, 101.8, 66.1, 65.0, 56.6, 56.3, 56.0, 55.9, 55.6, 43.0, 43.7, 15.8, 15.4. HRMS calcd. for $C_{20}H_{20}NaO_5$:

363.12029 (M+Na) found 363.12034



Crystal data and structure refinement for **34**.

Empirical formula	C20 H20 O5	
Formula weight	340.36	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.0150(6) Å	□= 80.854(3)°.
	b = 10.4826(7) Å	□= 86.762(2)°.
	c = 23.8587(19) Å	□ = 73.715(4)°.
Volume	1662.5(2) Å^3	
Z	4	
Density (calculated)	1.360 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	720	
Crystal size	0.22 x 0.10 x 0.04 mm	
Theta range for data collection	3.03 to 25.00°.	
Index ranges	-8<=h<=8, -12<=k<=12, -8<=l<=28	
Reflections collected	5854	
Independent reflections	5854	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	1.00 and 0.451
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5854 / 0 / 458
Goodness-of-fit on F^2	1.502
Final R indices [I>2sigma(I)]	R1 = 0.1329, wR2 = 0.2981
R indices (all data)	R1 = 0.1845, wR2 = 0.3223
Largest diff. peak and hole	0.650 and -0.661 e.$Å^{-3}$

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for 1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	5086(10)	-1964(7)	5389(3)	22(2)
C2	3275(10)	-1927(7)	5771(3)	19(2)
C3	3754(10)	-2054(6)	6409(3)	18(2)
C4	5288(11)	-3396(7)	6564(3)	24(2)
C5	4730(10)	-4512(7)	6745(3)	21(2)
C6	2600(10)	-4470(7)	6849(3)	22(2)
C7	1252(11)	-3131(7)	6900(3)	24(2)
C8	1875(10)	-1999(7)	6765(3)	22(2)
C9	845(11)	-771(8)	6972(3)	28(2)
C10	1734(11)	230(7)	6977(3)	23(2)
C11	3621(10)	228(7)	6699(3)	21(2)
C12	4420(11)	1299(7)	6655(3)	26(2)
C13	6119(11)	1331(7)	6317(3)	26(2)
C14	6935(11)	319(7)	5993(3)	24(2)
C15	6084(10)	-755(7)	6033(3)	20(2)
C16	4569(10)	-872(7)	6418(3)	22(2)
C17	7375(10)	-3353(7)	4806(3)	23(2)
C18	7416(11)	-4585(7)	4545(3)	32(2)
C19	8034(10)	-5913(7)	6801(3)	28(2)
C20	9259(12)	1455(7)	5525(3)	30(2)
C21	121(10)	-1676(7)	9626(3)	21(2)
C22	-1677(10)	-1359(7)	9244(3)	21(2)
C23	-1065(10)	-1097(7)	8599(3)	20(2)
C24	489(10)	-2370(7)	8470(3)	20(2)
C25	-70(10)	-3347(7)	8292(3)	17(2)
C26	-2157(10)	-3190(7)	8140(3)	21(2)
C27	-3436(10)	-1819(7)	8079(3)	24(2)
C28	-2894(10)	-783(7)	8238(3)	22(2)

Table 1 Continued

C29	-3898(11)	586(7)	8031(3)	24(2)
C30	-3007(10)	1577(7)	8010(3)	24(2)
C31	-1077(10)	1362(7)	8280(3)	21(2)
C32	-261(11)	2416(7)	8315(3)	24(2)
C33	1378(11)	2213(7)	8658(3)	27(2)
C34	2076(10)	1004(7)	9004(3)	21(2)
C35	1254(10)	-53(7)	8981(3)	18(2)
C36	-237(10)	109(7)	8588(3)	21(2)
C37	2274(10)	-3478(7)	10221(3)	23(2)
C38	2338(11)	-4911(7)	10474(3)	33(2)
C39	3252(10)	-4756(7)	8278(4)	29(2)
C40	4368(11)	1808(7)	9482(3)	29(2)
O1	6739(7)	-1696(5)	5671(2)	22(1)
O2	5776(7)	-3222(4)	5232(2)	22(1)
O3	5947(7)	-5806(5)	6855(2)	24(1)
O4	2057(7)	-5517(5)	6945(2)	32(1)
O5	8451(7)	313(4)	5607(2)	26(1)
O6	1804(7)	-1233(4)	9355(2)	22(1)
O7	792(7)	-3066(4)	9790(2)	21(1)
O8	1165(7)	-4582(4)	8210(2)	24(1)
O9	-2672(7)	-4146(5)	8014(2)	32(1)
O10	3567(7)	718(5)	9404(2)	25(1)

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Table 2. Bond lengths [Å] and angles [°] for 1.

C1-O2	1.376(8)	C17-C18	1.513(9)
C1-O1	1.485(8)	C17-H17A	0.99
C1-C2	1.515(9)	C17-H17B	0.99
C1-H1	1.00	C18-H18A	0.98
C2-C3	1.556(9)	C18-H18B	0.98
C2-H2A	0.99	C18-H18C	0.98
C2-H2B	0.99	C19-O3	1.437(8)
C3-C16	1.506(9)	C19-H19A	0.98
C3-C4	1.518(9)	C19-H19B	0.98
C3-C8	1.520(9)	C19-H19C	0.98
C4-C5	1.336(9)	C20-O5	1.445(7)
C4-H4	0.95	C20-H20A	0.98
C5-O3	1.379(8)	C20-H20B	0.98
C5-C6	1.490(9)	C20-H20C	0.98
C6-O4	1.244(8)	C21-O7	1.397(8)
C6-C7	1.475(10)	C21-O6	1.467(7)
C7-C8	1.362(10)	C21-C22	1.526(9)
C7-H7	0.95	C21-H21	1.00
C8-C9	1.437(10)	C22-C23	1.575(10)
C9-C10	1.365(10)	C22-H22A	0.99
C9-H9	0.95	C22-H22B	0.99
C10-C11	1.446(10)	C23-C28	1.515(9)
C10-H10	0.95	C23-C36	1.528(9)
C11-C12	1.376(10)	C23-C24	1.530(9)
C11-C16	1.410(10)	C24-C25	1.328(9)
C12-C13	1.407(10)	C24-H24	0.95
C12-H12	0.95	C25-O8	1.377(8)
C13-C14	1.387(10)	C25-C26	1.486(9)
C13-H13	0.95	C26-O9	1.239(8)
C14-O5	1.366(8)	C26-C27	1.456(10)
C14-C15	1.403(9)	C27-C28	1.359(9)
C15-O1	1.381(8)	C27-H27	0.95
C15-C16	1.383(10)	C28-C29	1.430(10)
C17-O2	1.463(8)	C29-C30	1.348(9)

Table 2 Continued

C29-H29	0.95	C37-C38	1.517(10)
C30-C31	1.477(10)	C37-H37A	0.99
C30-H30	0.95	C37-H37B	0.99
C31-C36	1.385(10)	C38-H38A	0.98
C31-C32	1.395(9)	C38-H38B	0.98
C32-C33	1.397(10)	C38-H38C	0.98
C32-H32	0.95	C39-O8	1.438(8)
C33-C34	1.375(10)	C39-H39A	0.98
C33-H33	0.95	C39-H39B	0.98
C34-C35	1.394(9)	C39-H39C	0.98
C34-O10	1.394(8)	C40-O10	1.448(7)
C35-O6	1.378(8)	C40-H40A	0.98
C35-C36	1.401(10)	C40-H40B	0.98
C37-O7	1.432(8)	C40-H40C	0.98

		Table 2 Continued	
O2-C1-O1	107.5(5)	C5-C4-H4	119.6
O2-C1-C2	108.9(6)	C3-C4-H4	119.6
O1-C1-C2	113.1(5)	C4-C5-O3	127.0(6)
O2-C1-H1	109.1	C4-C5-C6	121.5(6)
O1-C1-H1	109.1	O3-C5-C6	111.5(6)
C2-C1-H1	109.1	O4-C6-C7	122.9(6)
C1-C2-C3	112.5(6)	O4-C6-C5	121.4(6)
C1-C2-H2A	109.1	C7-C6-C5	115.3(6)
C3-C2-H2A	109.1	C8-C7-C6	121.2(6)
C1-C2-H2B	109.1	C8-C7-H7	119.4
C3-C2-H2B	109.1	C6-C7-H7	119.4
H2A-C2-H2B	107.8	C7-C8-C9	121.5(7)
C16-C3-C4	112.9(6)	C7-C8-C3	119.2(6)
C16-C3-C8	113.7(6)	C9-C8-C3	119.2(6)
C4-C3-C8	110.5(6)	C10-C9-C8	121.4(7)
C16-C3-C2	102.4(5)	C10-C9-H9	119.3
C4-C3-C2	107.0(5)	C8-C9-H9	119.3
C8-C3-C2	109.7(5)	C9-C10-C11	122.9(7)
C5-C4-C3	120.8(6)	C9-C10-H10	118.6

C11-C10-H10	118.6	H19A-C19-H19C	109.5
C12-C11-C16	119.2(7)	H19B-C19-H19C	109.5
		O5-C20-H20A	109.5
C12-C11-C10	122.8(6)	O5-C20-H20B	109.5
C16-C11-C10	117.6(6)	H20A-C20-H20B	109.5
C11-C12-C13	120.9(7)	O5-C20-H20C	109.5
C11-C12-H12	119.5	H20A-C20-H20C	109.5
C13-C12-H12	119.5	H20B-C20-H20C	109.5
C14-C13-C12	120.0(7)	O7-C21-O6	107.2(5)
C14-C13-H13	120.0	O7-C21-C22	109.1(6)
C12-C13-H13	120.0	O6-C21-C22	114.2(6)
O5-C14-C13	125.1(7)	O7-C21-H21	108.7
O5-C14-C15	116.4(6)	O6-C21-H21	108.7
C13-C14-C15	118.4(7)	C22-C21-H21	108.7
O1-C15-C16	119.3(6)	C21-C22-C23	110.9(6)
O1-C15-C14	119.1(6)	C21-C22-H22A	109.5
C16-C15-C14	121.5(7)	C23-C22-H22A	109.5
C15-C16-C11	118.8(6)	C21-C22-H22B	109.5
C15-C16-C3	116.2(6)	C23-C22-H22B	109.5
C11-C16-C3	123.5(6)	H22A-C22-H22B	108.0
O2-C17-C18	106.2(5)	C28-C23-C36	113.1(6)
O2-C17-H17A	110.5	C28-C23-C24	111.6(6)
C18-C17-H17A	110.5	C36-C23-C24	113.8(6)
O2-C17-H17B	110.5	C28-C23-C22	109.0(6)
C18-C17-H17B	110.5	C36-C23-C22	101.4(5)
H17A-C17-H17B	108.7	C24-C23-C22	107.2(5)
C17-C18-H18A	109.5	C25-C24-C23	120.3(6)
C17-C18-H18B	109.5	C25-C24-H24	119.8
H18A-C18-H18B	109.5	C23-C24-H24	119.8
C17-C18-H18C	109.5	C24-C25-O8	125.6(6)
H18A-C18-H18C	109.5	C24-C25-C26	122.2(6)
H18B-C18-H18C	109.5	O8-C25-C26	112.2(5)
O3-C19-H19A	109.5	O9-C26-C27	123.4(6)
O3-C19-H19B	109.5	O9-C26-C25	121.1(6)
H19A-C19-H19B	109.5	C27-C26-C25	115.0(6)
O3-C19-H19C	109.5	C28-C27-C26	123.2(7)

Table 2 Continued

C28-C27-H27	118.4	O7-C37-H37A	110.4
C26-C27-H27	118.4	C38-C37-H37A	110.4
C27-C28-C29	121.5(7)	O7-C37-H37B	110.4
C27-C28-C23	118.7(6)	C38-C37-H37B	110.4
C29-C28-C23	119.6(6)	H37A-C37-H37B	108.6
C30-C29-C28	121.7(7)	C37-C38-H38A	109.5
C30-C29-H29	119.2	C37-C38-H38B	109.5
C28-C29-H29	119.2	H38A-C38-H38B	109.5
C29-C30-C31	122.2(7)	C37-C38-H38C	109.5
C29-C30-H30	118.9	H38A-C38-H38C	109.5
C31-C30-H30	118.9	H38B-C38-H38C	109.5
C36-C31-C32	119.2(7)	O8-C39-H39A	109.5
C36-C31-C30	117.6(6)	O8-C39-H39B	109.5
C32-C31-C30	122.3(7)	H39A-C39-H39B	109.5
C31-C32-C33	120.4(7)	O8-C39-H39C	109.5
C31-C32-H32	119.8	H39A-C39-H39C	109.5
C33-C32-H32	119.8	H39B-C39-H39C	109.5
C34-C33-C32	119.8(6)	O10-C40-H40A	109.5
C34-C33-H33	120.1	O10-C40-H40B	109.5
C32-C33-H33	120.1	H40A-C40-H40B	109.5
C33-C34-C35	120.3(6)	O10-C40-H40C	109.5
C33-C34-O10	125.4(6)	H40A-C40-H40C	109.5
C35-C34-O10	114.3(6)	H40B-C40-H40C	109.5
O6-C35-C34	121.5(6)	C15-O1-C1	112.7(5)
O6-C35-C36	119.0(6)	C1-O2-C17	114.7(5)
C34-C35-C36	119.5(6)	C5-O3-C19	114.5(5)
C31-C36-C35	120.1(6)	C14-O5-C20	117.6(5)
C31-C36-C23	123.5(6)	C35-O6-C21	113.8(5)
C35-C36-C23	115.7(6)	C21-O7-C37	114.4(5)
O7-C37-C38	106.7(5)	C25-O8-C39	115.8(5)
		C34-O10-C40	117.0(5)

Table 3. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	24(4)	22(4)	23(4)	-7(3)	-1(3)	-10(3)
C2	18(4)	16(4)	26(4)	-8(3)	1(3)	-5(3)
C3	11(4)	11(3)	34(4)	-10(3)	0(3)	-4(3)
C4	17(4)	24(4)	31(4)	-1(3)	-3(3)	-9(3)
C5	9(4)	14(4)	38(5)	-3(3)	-3(3)	-2(3)
C6	19(4)	24(4)	28(4)	-4(3)	6(3)	-18(3)
C7	13(4)	32(5)	27(4)	-6(3)	-2(3)	-4(3)
C8	10(4)	21(4)	29(4)	-1(3)	0(3)	2(3)
C9	20(4)	32(5)	28(5)	-3(4)	-3(3)	-1(4)
C10	22(4)	19(4)	22(4)	-7(3)	3(3)	4(3)
C11	14(4)	15(4)	30(4)	-5(3)	-6(3)	3(3)
C12	25(4)	21(4)	30(5)	-13(3)	-5(3)	4(4)
C13	30(4)	12(4)	38(5)	-2(3)	-13(4)	-8(3)
C14	19(4)	24(4)	32(5)	-9(4)	0(3)	-6(3)
C15	22(4)	11(4)	27(4)	-2(3)	-3(3)	-7(3)
C16	18(4)	20(4)	28(4)	-3(3)	-5(3)	-6(3)
C17	15(4)	27(4)	33(4)	-11(3)	4(3)	-14(3)
C18	15(4)	36(5)	54(6)	-25(4)	14(4)	-14(4)
C19	13(4)	16(4)	56(6)	-3(4)	-5(3)	-4(3)
C20	35(5)	21(4)	42(5)	-2(4)	-6(4)	-22(4)
C21	14(4)	23(4)	31(4)	-5(3)	7(3)	-14(3)
C22	17(4)	26(4)	20(4)	0(3)	-4(3)	-9(3)
C23	10(4)	16(4)	34(5)	-7(3)	-6(3)	1(3)
C24	15(4)	25(4)	23(4)	-3(3)	5(3)	-14(3)
C25	10(4)	21(4)	23(4)	-4(3)	-2(3)	-9(3)
C26	10(4)	30(4)	25(4)	-6(3)	3(3)	-7(3)
C27	12(4)	37(5)	26(4)	-2(4)	-3(3)	-12(4)
C28	11(4)	25(4)	30(4)	-7(3)	4(3)	-2(3)
C29	15(4)	28(4)	29(4)	-5(3)	1(3)	-6(3)
C30	20(4)	23(4)	25(4)	-2(3)	1(3)	-2(3)
C31	18(4)	21(4)	27(4)	-9(3)	1(3)	-9(3)

Table 3 Continued

C32	25(4)	18(4)	31(4)	2(3)	-1(3)	-11(3)
C33	28(4)	22(4)	37(5)	-9(4)	10(4)	-18(4)
C34	17(4)	22(4)	28(4)	-6(3)	-1(3)	-12(3)
C35	20(4)	17(4)	21(4)	0(3)	-1(3)	-11(3)
C36	20(4)	11(4)	34(5)	-11(3)	6(3)	-6(3)
C37	23(4)	30(4)	25(4)	-3(3)	-4(3)	-21(4)
C38	24(4)	28(4)	46(5)	7(4)	-7(4)	-13(4)
C39	8(4)	23(4)	55(6)	-1(4)	0(3)	-5(3)
C40	33(5)	23(4)	39(5)	-12(4)	3(4)	-19(4)
O1	16(3)	24(3)	32(3)	-8(2)	-3(2)	-14(2)
O2	17(3)	18(3)	33(3)	-8(2)	7(2)	-7(2)
O3	15(3)	19(3)	45(3)	-3(2)	-3(2)	-14(2)
O4	25(3)	34(3)	45(3)	-15(3)	6(2)	-18(3)
O5	26(3)	15(3)	41(3)	-5(2)	0(2)	-16(2)
O6	13(3)	22(3)	34(3)	3(2)	1(2)	-13(2)
O7	21(3)	14(3)	30(3)	3(2)	-5(2)	-11(2)
O8	13(3)	19(3)	41(3)	-8(2)	3(2)	-6(2)
O9	23(3)	36(3)	42(3)	-6(3)	-2(2)	-17(3)
O10	20(3)	25(3)	36(3)	-8(2)	-1(2)	-16(2)

Table 4. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 1.

	x	y	z	U(eq)
H1	4699	-1283	5042	26
H2A	2727	-2672	5716	23
H2B	2246	-1072	5658	23
H4	6661	-3443	6532	28
H7	-75	-3057	7030	29
H9	-483	-652	7108	34
H10	1086	960	7172	28
H12	3816	2026	6856	32
H13	6708	2047	6311	31
H17A	8662	-3465	4985	27
H17B	7113	-2545	4512	27
H18A	7499	-5351	4846	49
H18B	8574	-4787	4291	49
H18C	6201	-4414	4328	49
H19A	8333	-5535	6414	43
H19B	8792	-6861	6878	43
H19C	8402	-5416	7073	43
H20A	8192	2280	5420	45
H20B	10266	1356	5221	45
H20C	9868	1505	5878	45
H21	-295	-1238	9972	26
H22A	-2688	-554	9343	25
H22B	-2275	-2122	9307	25
H24	1859	-2462	8516	24
H27	-4714	-1639	7921	29
H29	-5228	802	7906	29
H30	-3642	2443	7814	28
H32	-824	3278	8105	29

Table 4 Continued

H33	2009	2907	8653	32
H37A	1926	-2885	10517	27
H37B	3584	-3435	10054	27
H38A	1058	-4930	10657	49
H38B	3394	-5255	10756	49
H38C	2603	-5475	10172	49
H39A	3516	-4747	8676	43
H39B	3651	-4023	8038	43
H39C	4010	-5617	8166	43
H40A	5055	2077	9134	43
H40B	5308	1509	9797	43
H40C	3284	2574	9570	43

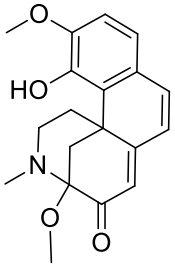
Table 5. Torsion angles [°] for 1.

O2-C1-C2-C3	102.0(6)	O5-C14-C15-O1	-3.2(10)
O1-C1-C2-C3	-17.5(8)	C13-C14-C15-O1	173.2(6)
C1-C2-C3-C16	58.5(7)	O5-C14-C15-C16	178.6(6)
C1-C2-C3-C4	-60.5(7)	C13-C14-C15-C16	-5.1(11)
C1-C2-C3-C8	179.6(6)	O1-C15-C16-C11	-166.6(6)
C16-C3-C4-C5	159.5(7)	C14-C15-C16-C11	11.7(11)
C8-C3-C4-C5	30.9(9)	O1-C15-C16-C3	0.4(10)
C2-C3-C4-C5	-88.5(8)	C14-C15-C16-C3	178.6(6)
C3-C4-C5-O3	174.3(7)	C12-C11-C16-C15	-10.2(10)
C3-C4-C5-C6	-5.3(11)	C10-C11-C16-C15	163.8(7)
C4-C5-C6-O4	170.4(7)	C12-C11-C16-C3	-176.2(7)
O3-C5-C6-O4	-9.2(10)	C10-C11-C16-C3	-2.1(10)
C4-C5-C6-C7	-16.8(11)	C4-C3-C16-C15	63.0(8)
O3-C5-C6-C7	163.5(6)	C8-C3-C16-C15	-170.1(6)
O4-C6-C7-C8	-176.7(7)	C2-C3-C16-C15	-51.8(8)
C5-C6-C7-C8	10.6(11)	C4-C3-C16-C11	-130.8(7)
C6-C7-C8-C9	-160.3(7)	C8-C3-C16-C11	-3.8(10)
C6-C7-C8-C3	17.0(11)	C2-C3-C16-C11	114.5(7)
C16-C3-C8-C7	-164.9(6)	O7-C21-C22-C23	-100.2(6)
C4-C3-C8-C7	-36.6(9)	O6-C21-C22-C23	19.8(8)
C2-C3-C8-C7	81.1(8)	C21-C22-C23-C28	-179.8(6)
C16-C3-C8-C9	12.5(9)	C21-C22-C23-C36	-60.3(7)
C4-C3-C8-C9	140.7(6)	C21-C22-C23-C24	59.3(7)
C2-C3-C8-C9	-101.5(7)	C28-C23-C24-C25	-29.5(9)
C7-C8-C9-C10	161.2(7)	C36-C23-C24-C25	-159.0(6)
C3-C8-C9-C10	-16.1(10)	C22-C23-C24-C25	89.7(7)
C8-C9-C10-C11	10.0(11)	C23-C24-C25-O8	-173.9(6)
C9-C10-C11-C12	173.2(7)	C23-C24-C25-C26	8.0(10)
C9-C10-C11-C16	-0.7(10)	C24-C25-C26-O9	-174.9(7)
C16-C11-C12-C13	2.4(11)	O8-C25-C26-O9	6.8(10)
C10-C11-C12-C13	-171.3(6)	C24-C25-C26-C27	12.9(10)
C11-C12-C13-C14	4.3(11)	O8-C25-C26-C27	-165.4(6)
C12-C13-C14-O5	173.0(7)	O9-C26-C27-C28	177.4(7)
C12-C13-C14-C15	-3.0(11)	C25-C26-C27-C28	-10.6(10)

Table 5 Continued

C26-C27-C28-C29	161.8(7)	C24-C23-C36-C35	-61.1(8)
C26-C27-C28-C23	-12.5(11)	C22-C23-C36-C35	53.7(7)
C36-C23-C28-C27	161.3(6)	C16-C15-O1-C1	47.5(8)
C24-C23-C28-C27	31.4(9)	C14-C15-O1-C1	-130.8(7)
C22-C23-C28-C27	-86.8(8)	O2-C1-O1-C15	-156.4(5)
C36-C23-C28-C29	-13.1(9)	C2-C1-O1-C15	-36.1(8)
C24-C23-C28-C29	-143.0(6)	O1-C1-O2-C17	-64.3(7)
C22-C23-C28-C29	98.8(7)	C2-C1-O2-C17	172.7(5)
C27-C28-C29-C30	-155.7(7)	C18-C17-O2-C1	-160.6(6)
C23-C28-C29-C30	18.5(11)	C4-C5-O3-C19	4.4(11)
C28-C29-C30-C31	-10.0(11)	C6-C5-O3-C19	-176.0(6)
C29-C30-C31-C36	-3.4(10)	C13-C14-O5-C20	-0.6(10)
C29-C30-C31-C32	-172.4(7)	C15-C14-O5-C20	175.5(6)
C36-C31-C32-C33	-0.2(11)	C34-C35-O6-C21	130.9(7)
C30-C31-C32-C33	168.7(7)	C36-C35-O6-C21	-45.9(8)
C31-C32-C33-C34	-6.1(11)	O7-C21-O6-C35	155.6(5)
C32-C33-C34-C35	5.0(11)	C22-C21-O6-C35	34.6(8)
C32-C33-C34-O10	-173.5(6)	O6-C21-O7-C37	65.2(7)
C33-C34-C35-O6	-174.3(6)	C22-C21-O7-C37	-170.6(5)
O10-C34-C35-O6	4.3(9)	C38-C37-O7-C21	162.4(6)
C33-C34-C35-C36	2.5(10)	C24-C25-O8-C39	-5.8(10)
O10-C34-C35-C36	-178.9(6)	C26-C25-O8-C39	172.4(6)
C32-C31-C36-C35	7.7(10)	C33-C34-O10-C40	3.5(10)
C30-C31-C36-C35	-161.7(6)	C35-C34-O10-C40	-175.0(6)
C32-C31-C36-C23	177.3(6)		
C30-C31-C36-C23	7.9(10)		
O6-C35-C36-C31	168.0(6)		
C34-C35-C36-C31	-8.9(11)		
O6-C35-C36-C23	-2.4(9)		
C34-C35-C36-C23	-179.2(6)		
C28-C23-C36-C31	0.2(10)		
C24-C23-C36-C31	129.0(7)		
C22-C23-C36-C31	-116.3(7)		
C28-C23-C36-C35	170.2(6)		

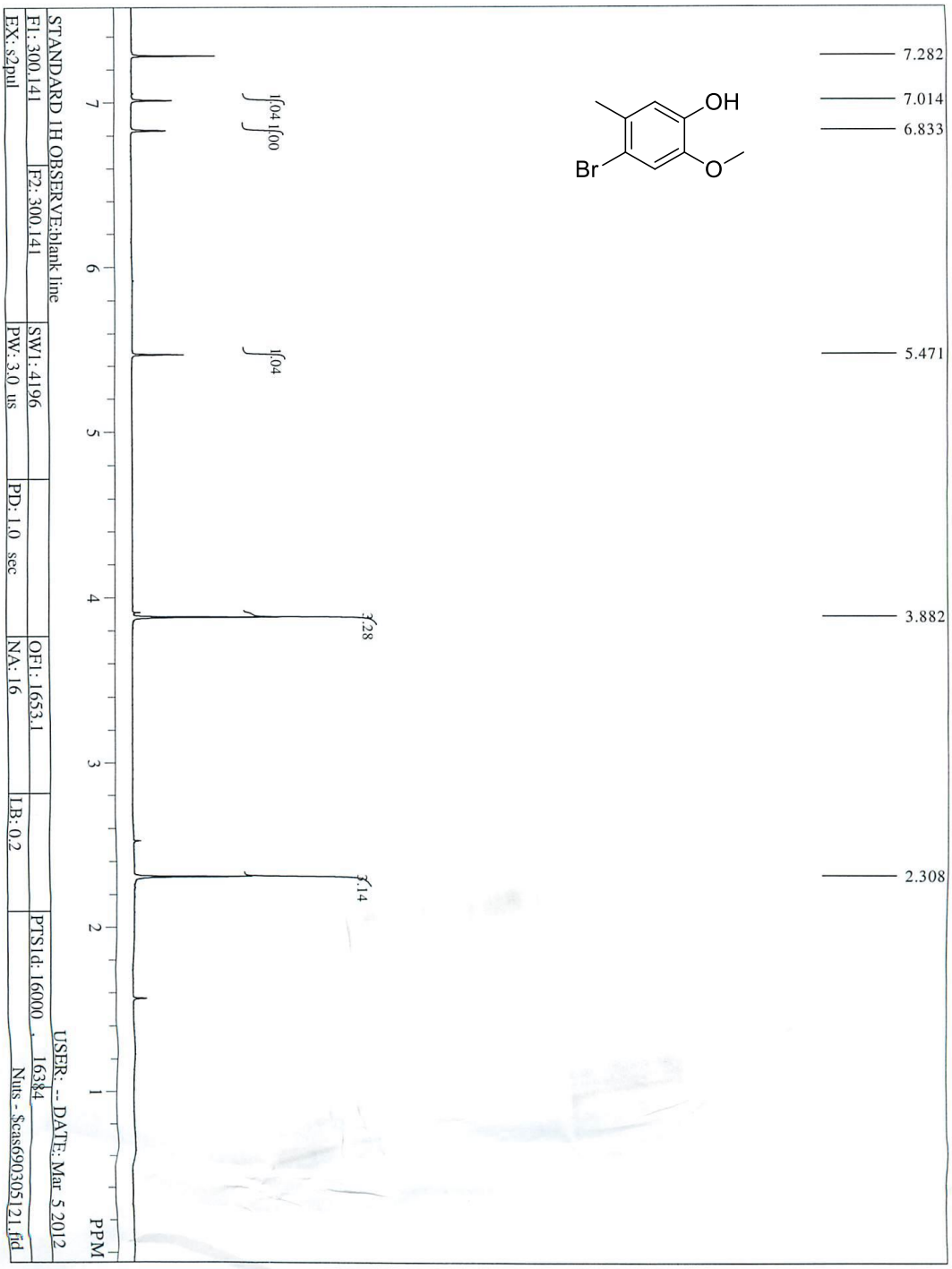
Cepharatine A (3)



(6) (50 mg, 0.14 mmol) was added to a mixture of dioxane:water (1 mL: 0.05 mL) and amberlyst 15 (10 mg). The solution was allowed to stir overnight or until disappearance of starting material was observed by TLC. The amberlyst was removed from the solution by filtration. Methylamine Hydrochloride (500 mg, 7.4 mmol), pre-dissolved in 1.33 mL of water, was added and allowed to stir for five minutes. Three portions of triacetoxyborohydride (75 mg, 0.35) were added every 15 minutes. After three hours, the solvent was removed *in vacuo* and the amine was rudimentarily purified by preparative TLC (7:93 MeOH:CH_2Cl_2). The impure amine was then dissolved in water (2 mL) and 1*M* HCl (.1 mL) was subsequently added. The solution was refluxed for 3 hours or until disappearance of starting material was observed by TLC. The solution was cooled and basified using saturated $NaHCO_3$. The solvent was removed *in vacuo* and the compound was purified by preparative TLC (7:93 MeOH:CH_2Cl_2) to afford Cepharatine A (20 mg, 42% over two steps) as a yellow solid. IR (thin film): 3424.7, 1642.8, 1562.0, 1482.5, 1272.6, 1075.61 ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (2H, s), 6.71 (1H, d, J = 9.6), 6.31 (1H, d, J = 9.2), 6.13 (1H, s), 3.95 (3H, s), 2.71 (1H, m), 2.67 (2H, m), 2.26 (4H, s), 1.40 (1H, s), 1.37 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 193.9, 161.5, 148.1, 144.4, 136.1,

125.6, 125.4, 124.0, 123.4, 121.3, 108.7, 83.3, 56.1, 46.6, 44.3, 43.4, 36.2, 31.3. HRMS calcd. for $C_{18}H_{20}NO_4$: 314.13868 (M+Na) found 314.1386

Appendix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7
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5
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3
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1
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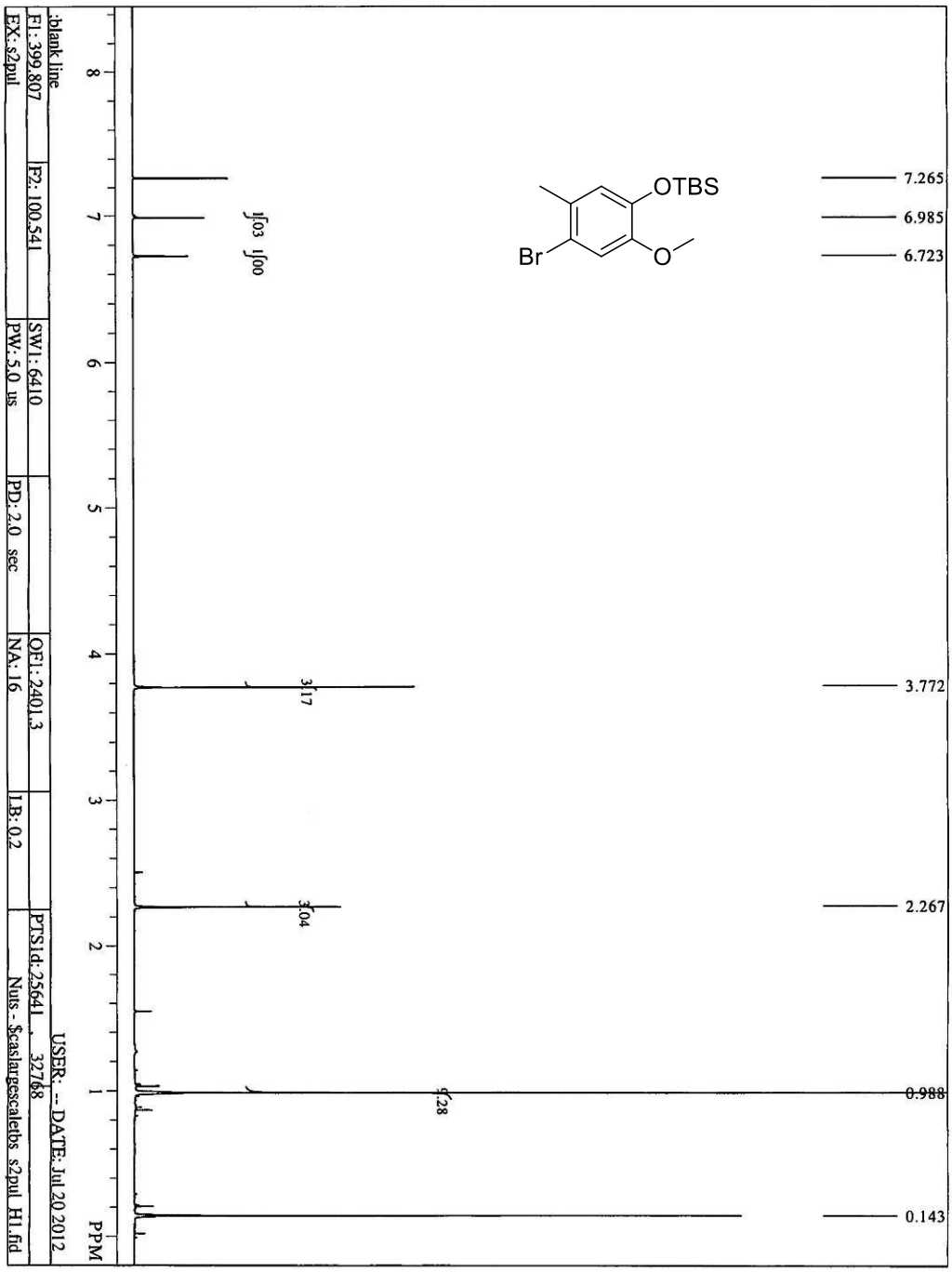
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3.04
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SW1: 6410
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PD: 2.0 sec
QF1: 2401.3
NA: 16
LB: 0.2
PTS1d: 25641
32768
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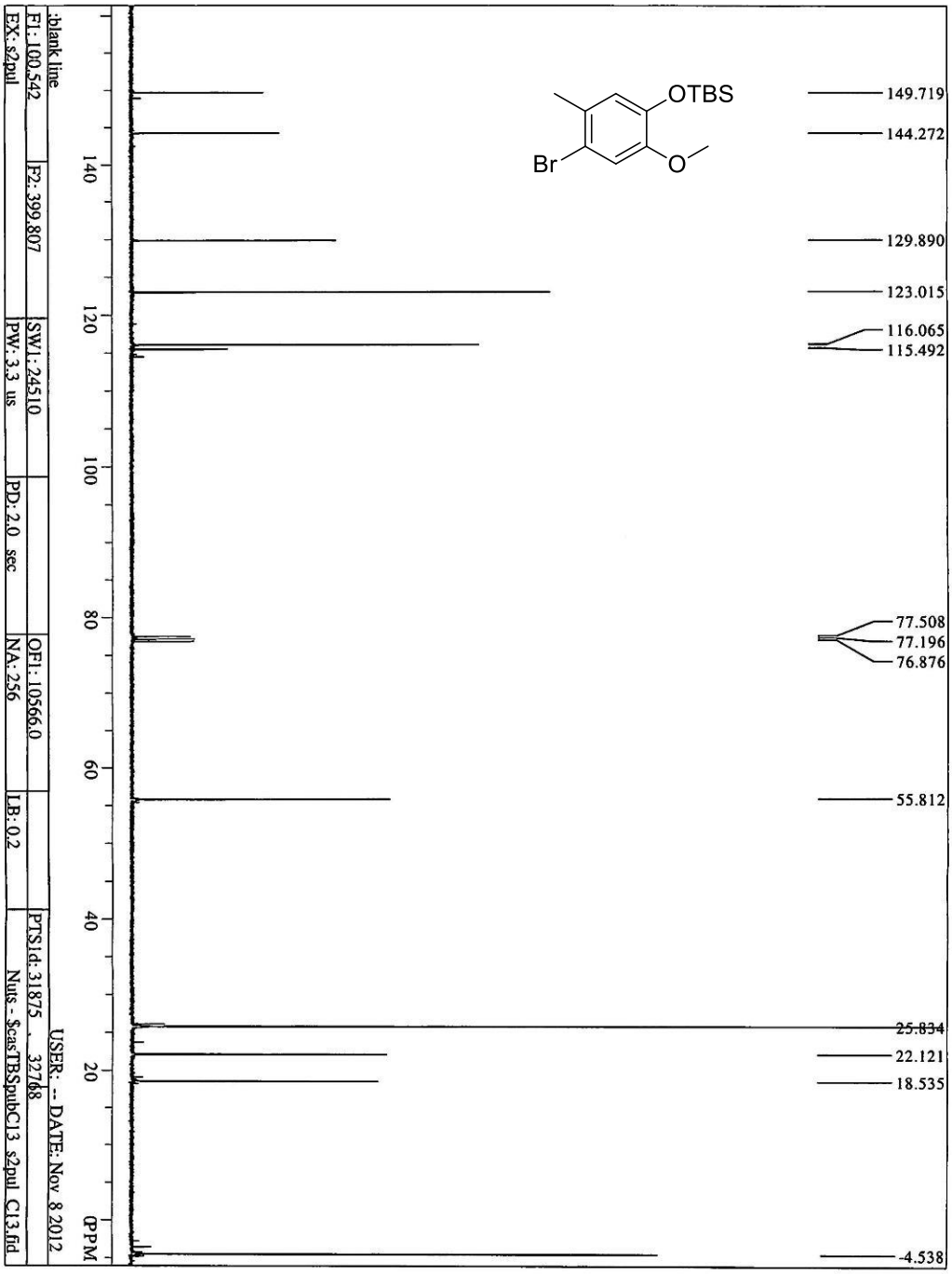
USER: -- DATE: Jul 20 2012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120
100
80
60
40
20
0
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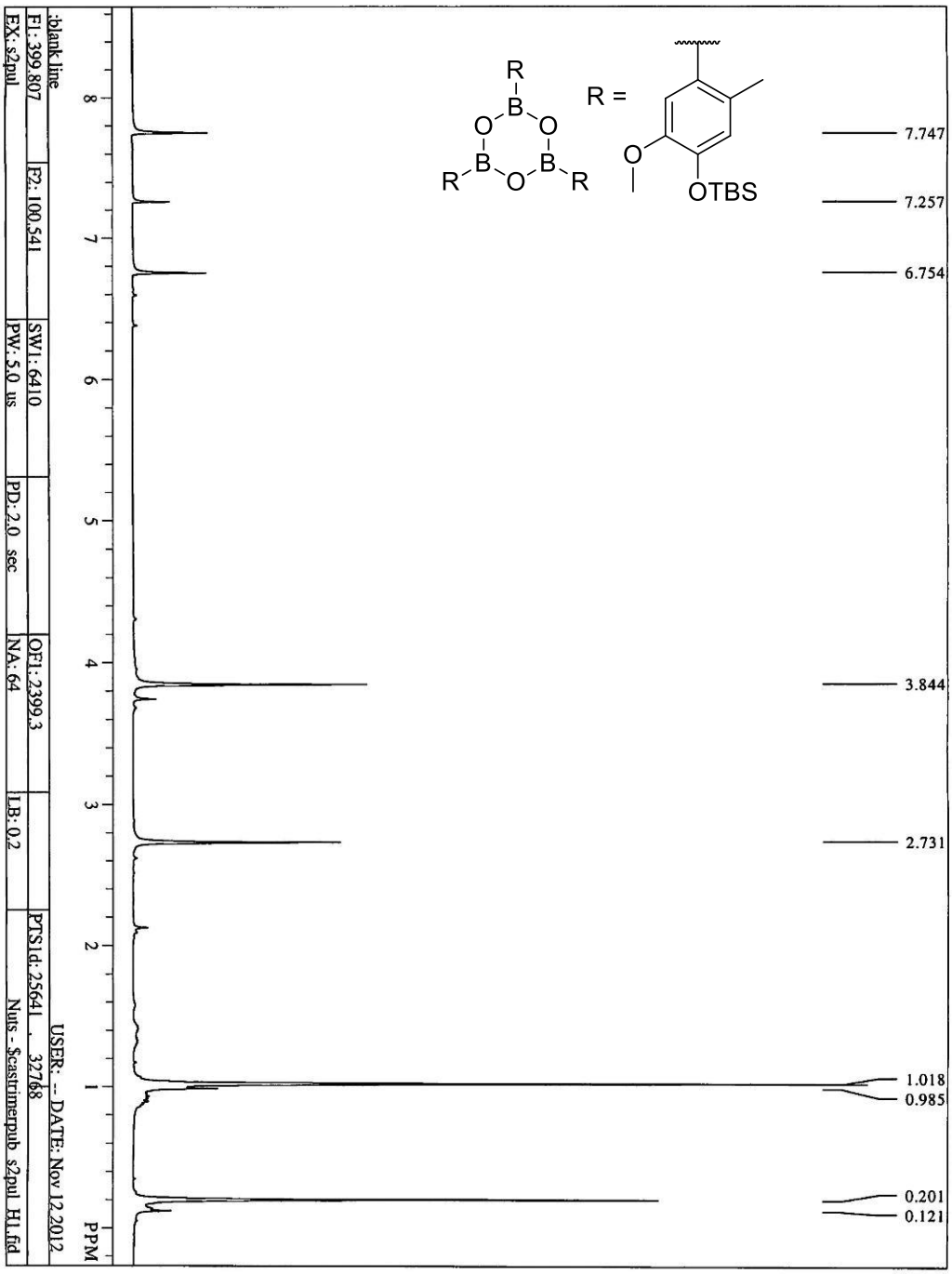
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B
O
B
R
R
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0.121
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7
6
5
4
3
2
1
PPM
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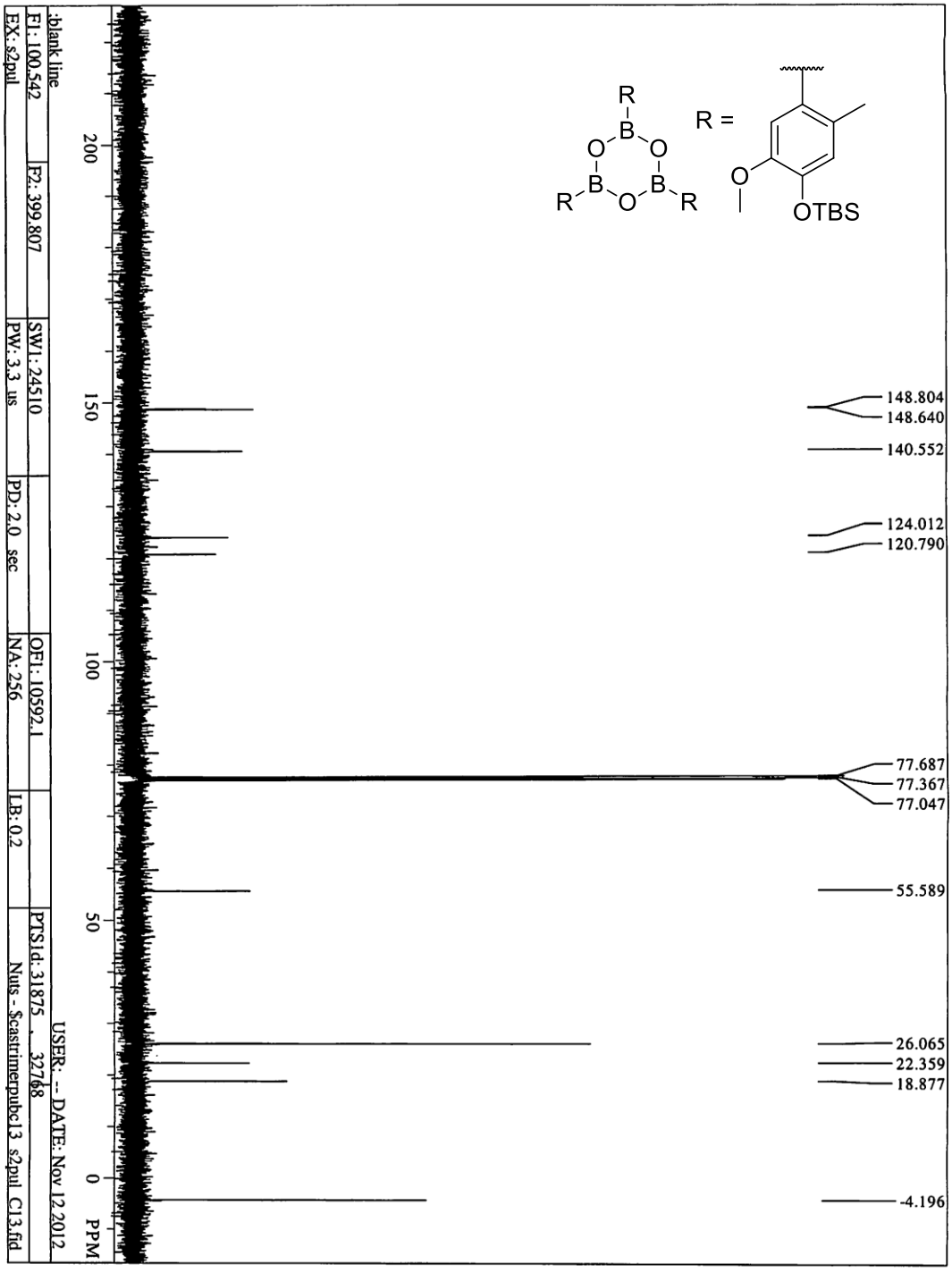
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B
B
O
R
R
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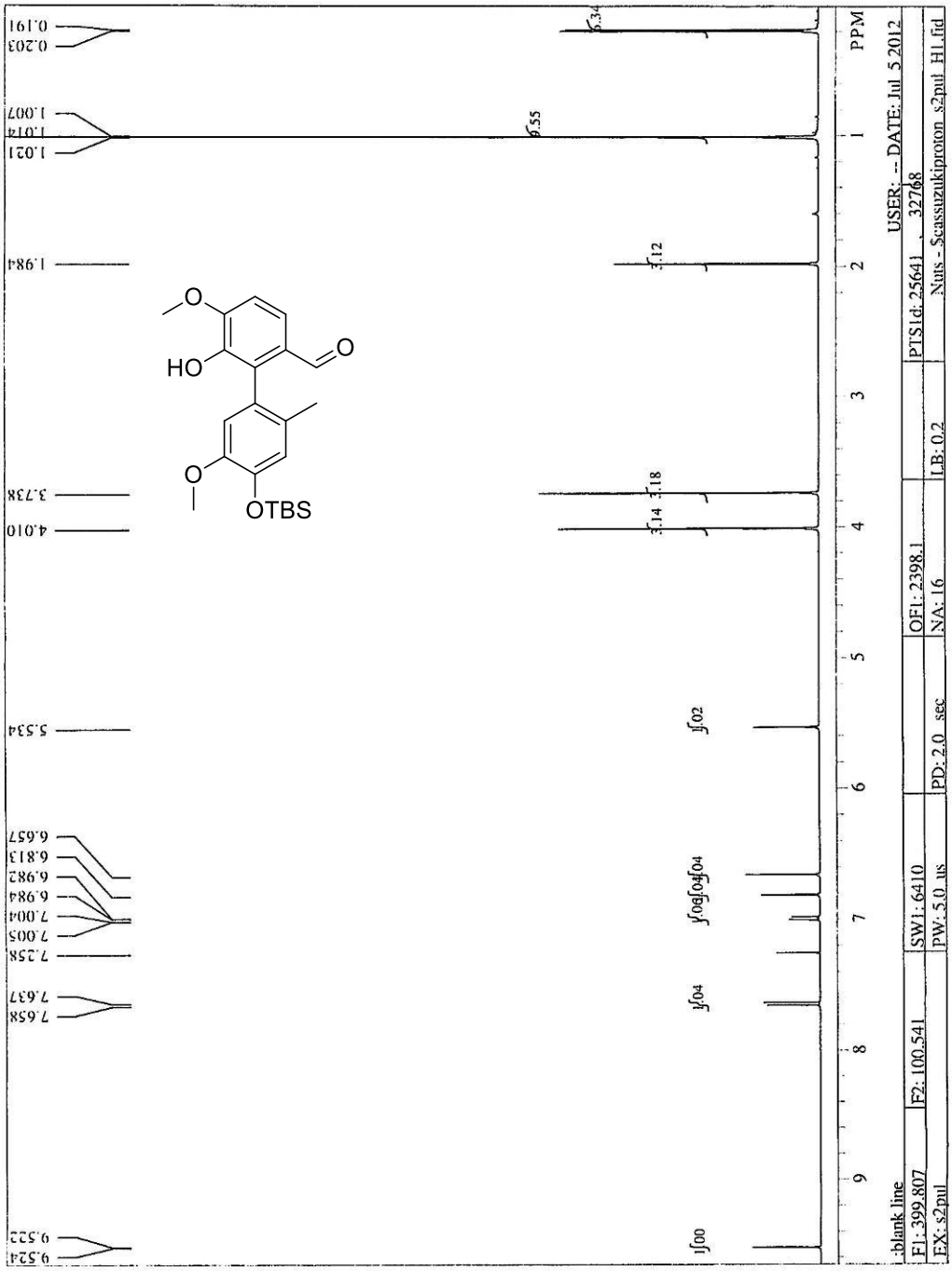
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7.004
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6.982
6.813
6.657
5.534
4.010
3.738
1.984
1.021
1.014
1.007
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0.191
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6.55
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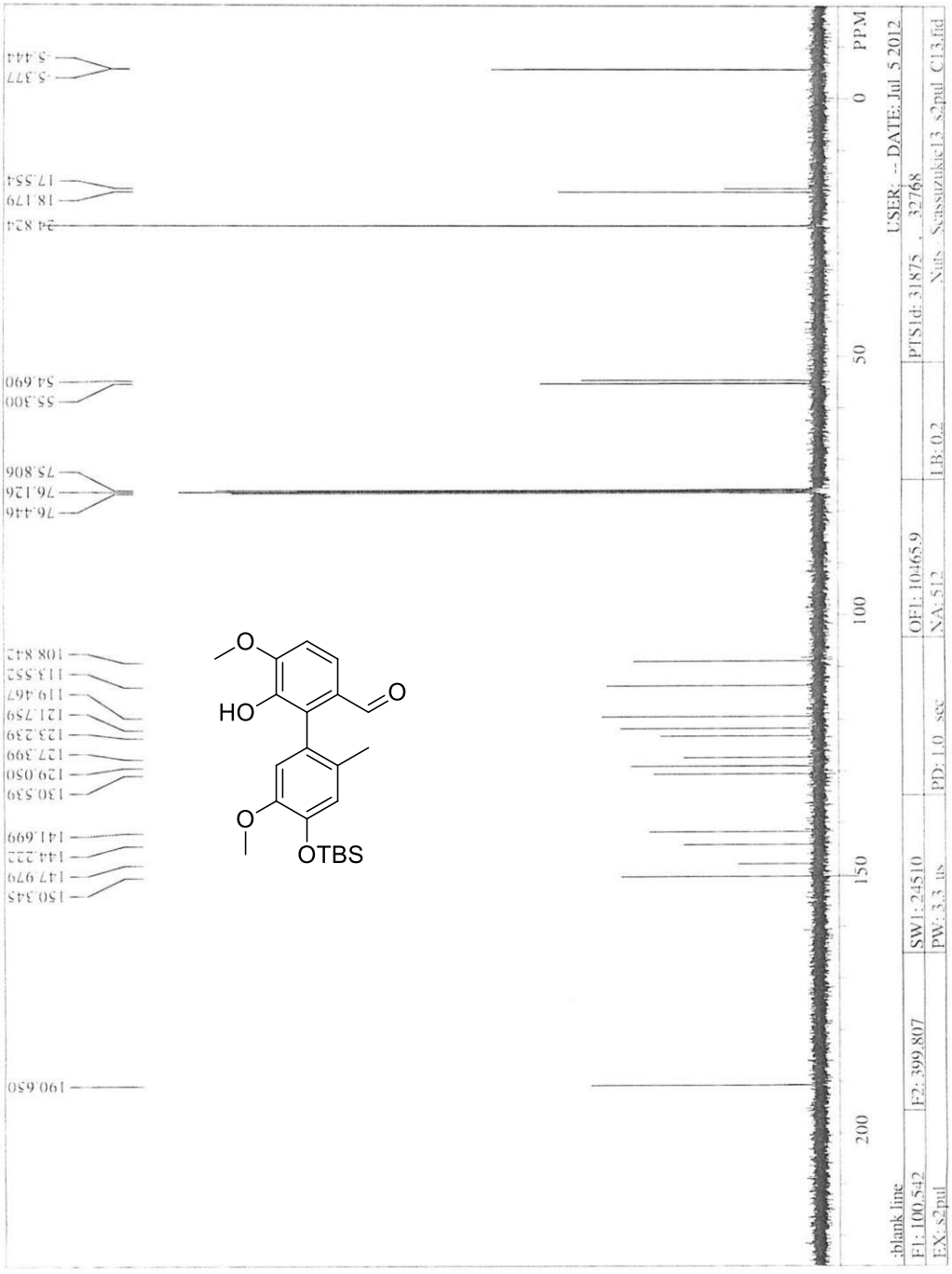
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121.759
123.239
127.399
129.050
130.539
141.699
144.222
147.979
150.345
190.650
HO
O
O
O
OTBS
PPM
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100
150
200
USER; -- DATE: Jul 5 2012
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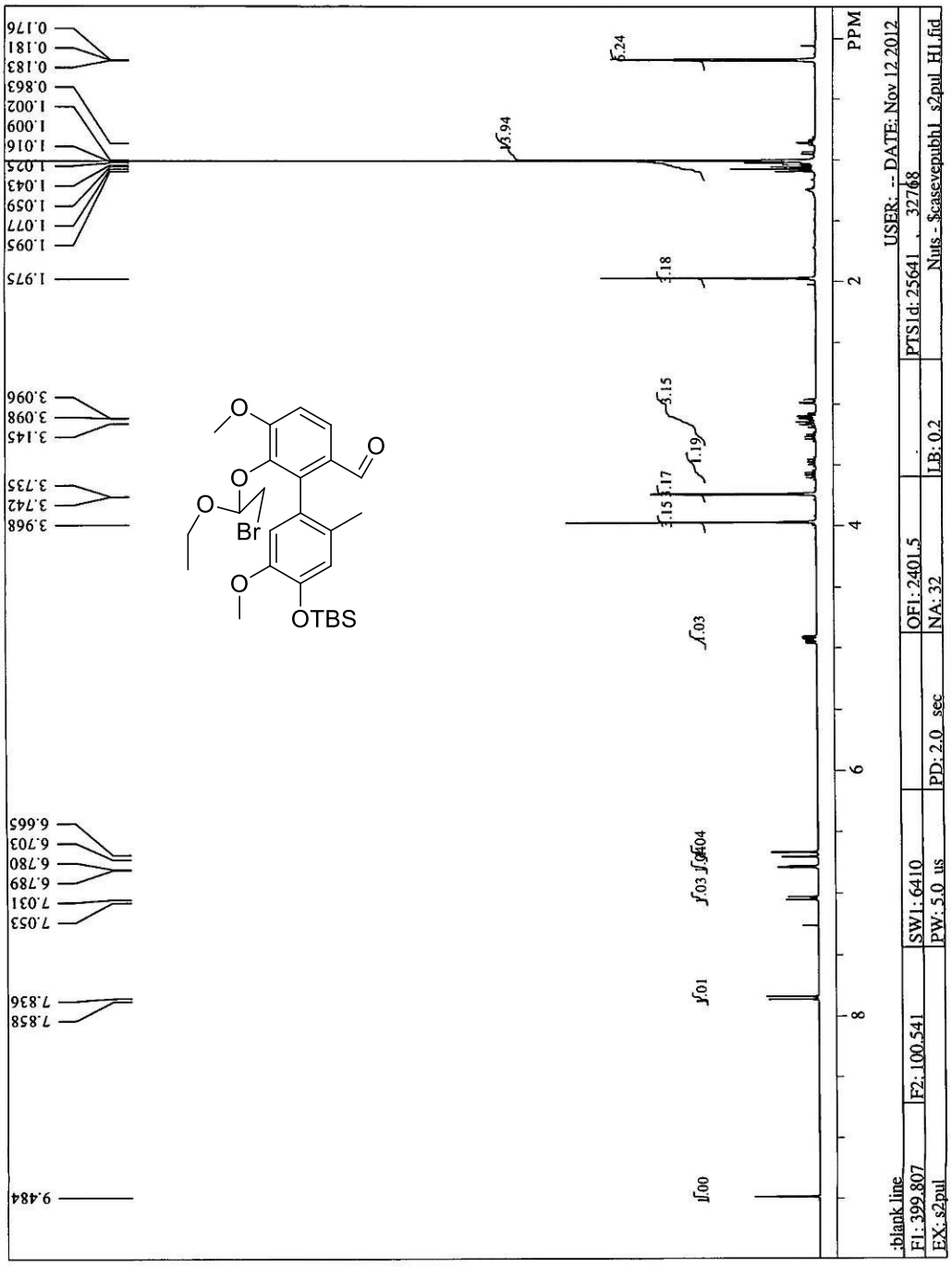
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3.096
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1.059
1.043
1.025
1.016
1.009
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5.24
5.18
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1.01
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1.03
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4
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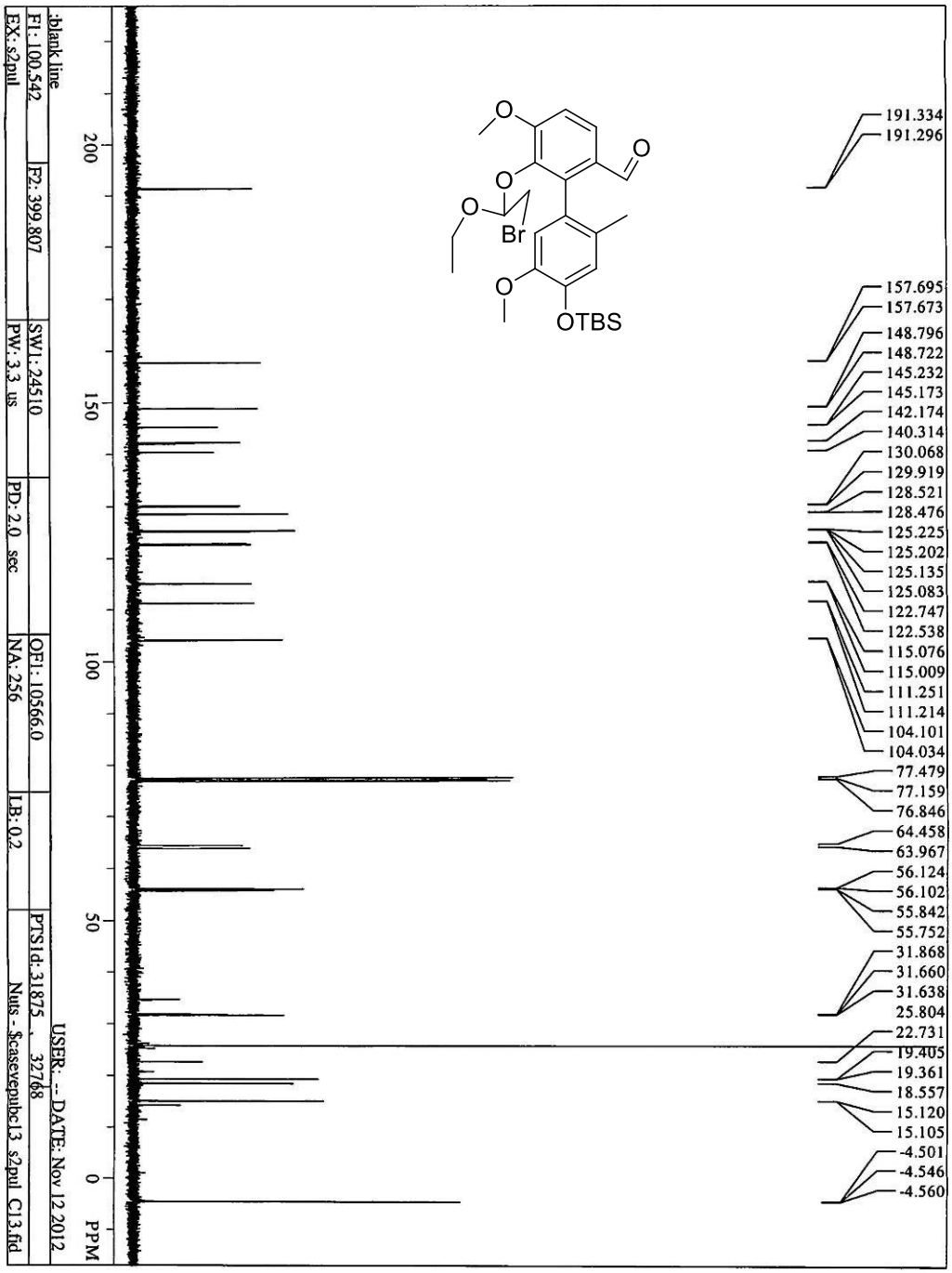
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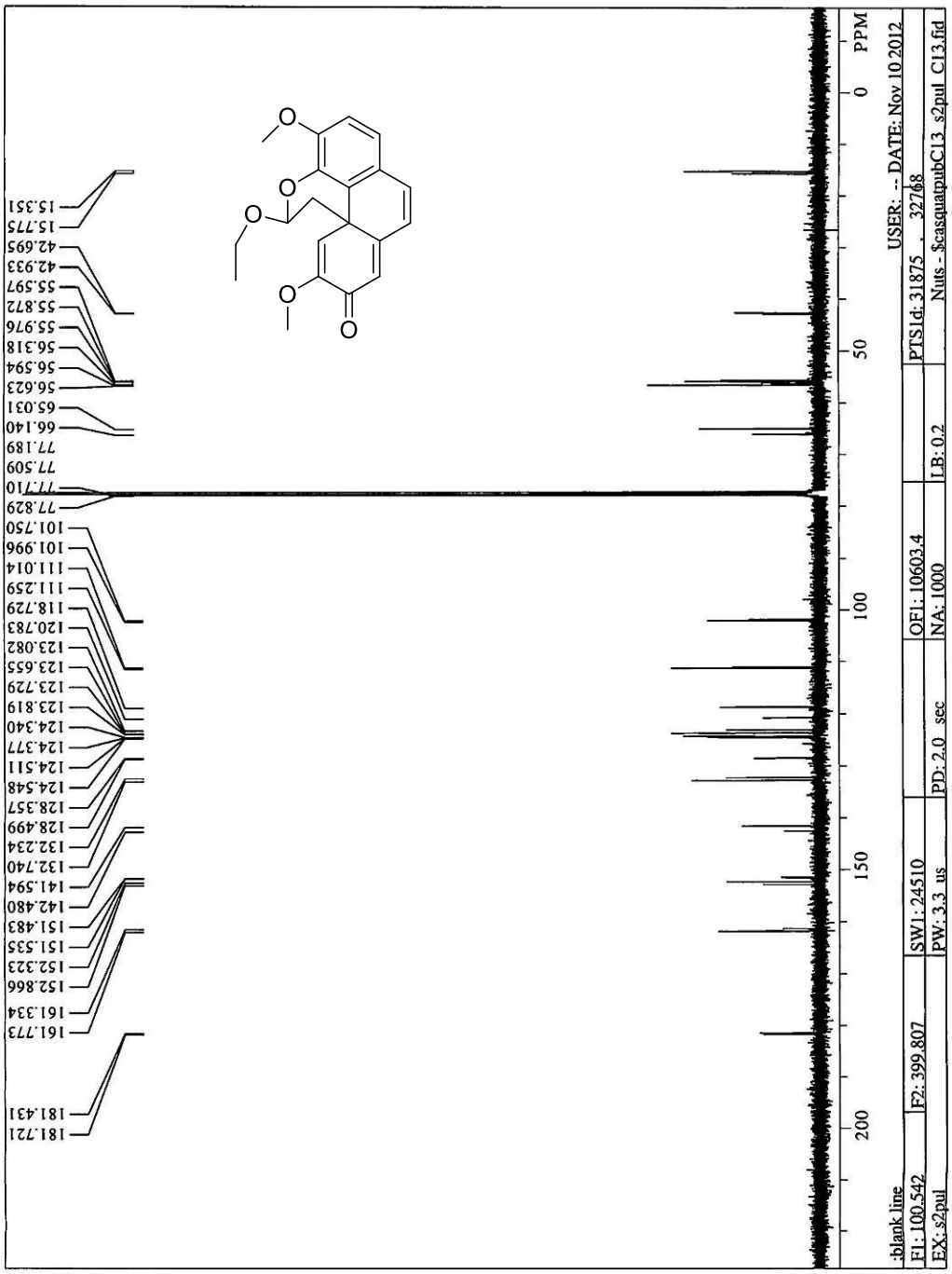
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123.729
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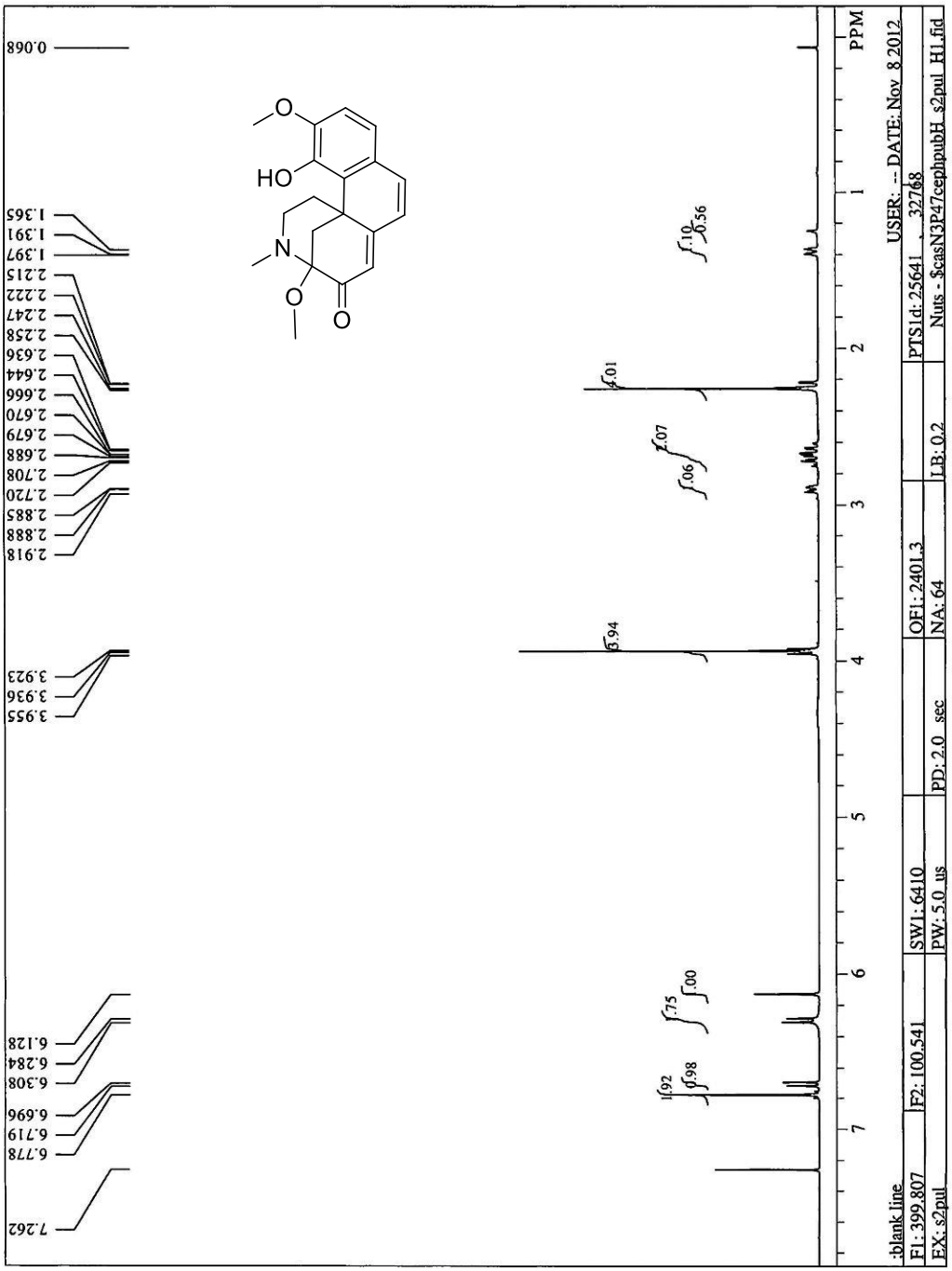
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2.888
2.918
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6.308
6.696
6.719
6.778
7.262
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O
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1.10
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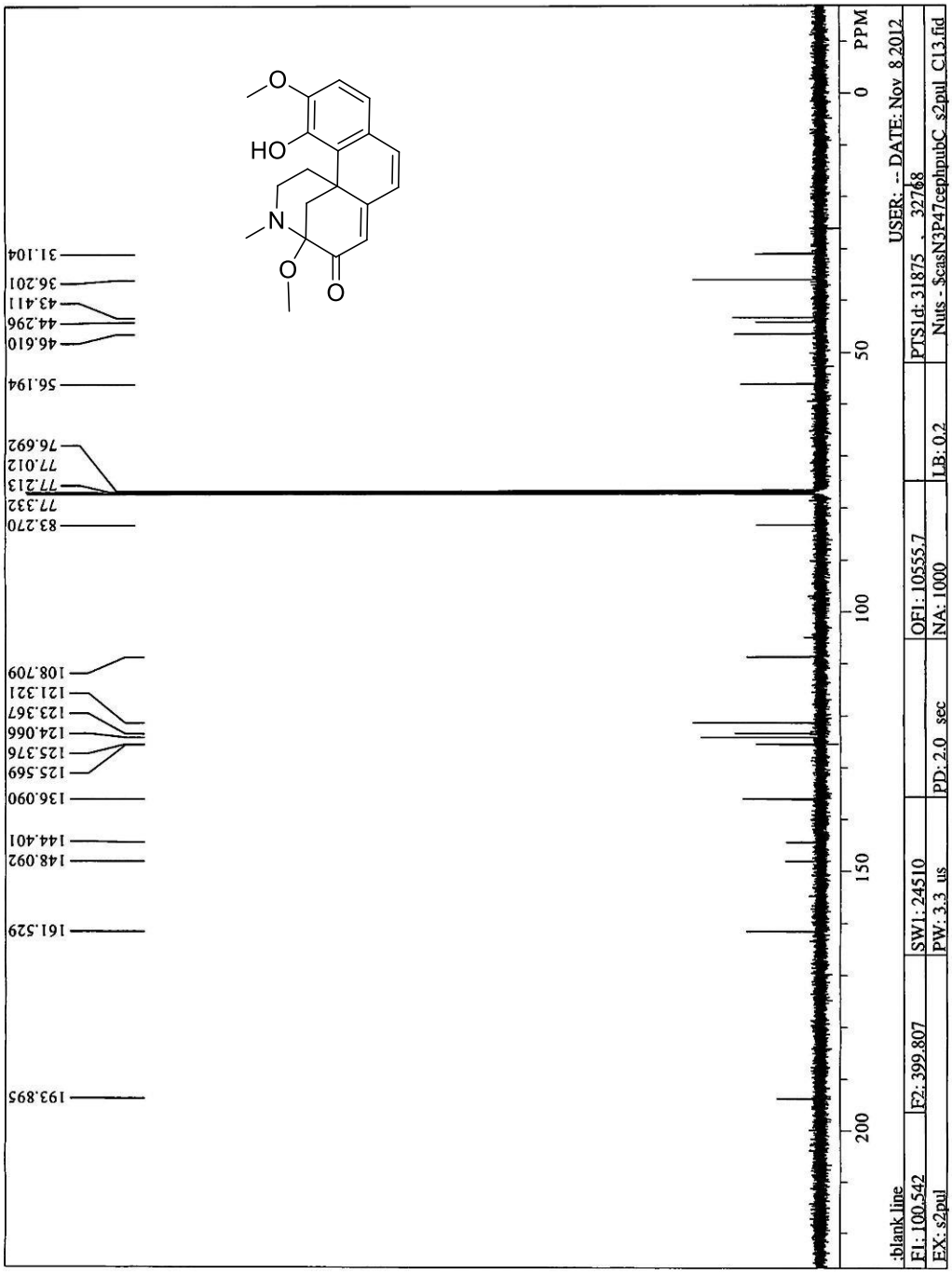
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50
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References

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